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No. 1

## PNEUMONIA AND SOME OF ITS COMPLICATIONS AT CAMP BOWIE

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The 2,344 cases of pneumonia and the various complications at the base hospital at Camp Bowie may be grouped into three periods.

PERIOD 1.—From the opening of the base hospital, Sept. 24, 1917, to Jan. 1, 1918: During this period occurred an epidemic of measles, with a large incidence of pneumonia, followed by numerous serious complications and a high death rate.

PERIOD 2.—From Jan. 1, to Sept. 27, 1918: The first three and a half months of this period continued to show a high incidence of pneumonia, though the number and severity of the complications was not as great as in Period 1. From April 15 to September 27 was a comparatively quiet period.

PERIOD 3.—From Sept. 28, 1918, to Jan. 1, 1919: This period included a very high incidence of influenza and a high percentage of pneumonia. In contrast to the pneumonia of 1917, there were comparatively few complications, and these were of a less virulent type.

### PERIOD 1

There were 3,624 cases of measles during Period 1\* (Chart 1). In addition to the measles there was a widespread infection of the upper respiratory tract throughout the camp. There were 973 cases of pneumonia, and in only 363 of these could we obtain a history of measles within a month preceding the development of the pneumonia. During the epidemic there may have been in camp a number of cases of abortive measles, unrecognized at the time, in which pneumonia developed later.

---

\* Figures given in all charts and tables are as of date of admission, and not of diagnosis or development of complications.

There were 237 deaths among these pneumonia cases, a mortality of 24.4 per cent. (Chart 2). In 17 per cent. of the pneumonia cases empyema developed, with a mortality of 32.5 per cent.

It will be seen from Chart 1 that the first peak was not reached until two weeks after the beginning of the measles epidemic; a much longer time than in the case of the influenza epidemic. There was then a diminution in the number of cases, but following the arrival of 6,000 draft troops, a second peak, almost as great, occurred two weeks after the first. There was a steady decline for ten days thereafter, when the admissions gradually ceased.

The pneumonia curve does not follow that of measles so closely as in the later influenza epidemic. The first pneumonia peak followed the first measles peak by ten days; six days after the second measles peak there was a rise in the number of cases of pneumonia.

TABLE 1.—BACTERIOLOGY OF PNEUMONIA DURING PERIOD 1 (DEC. 6-15, 1917)

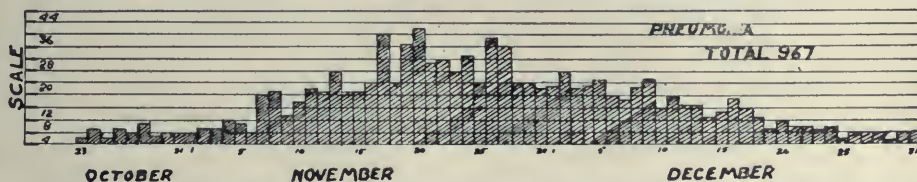
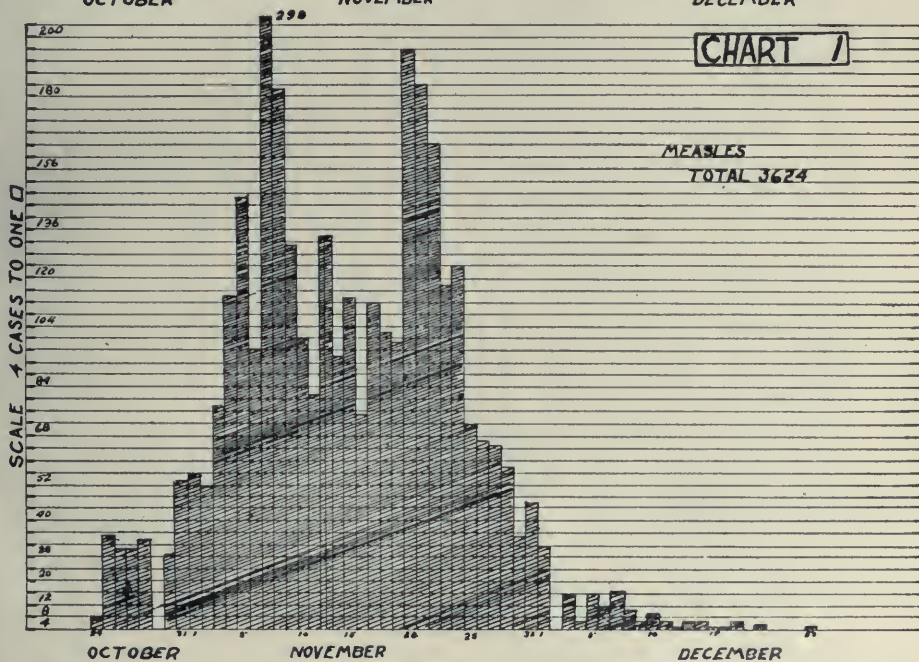
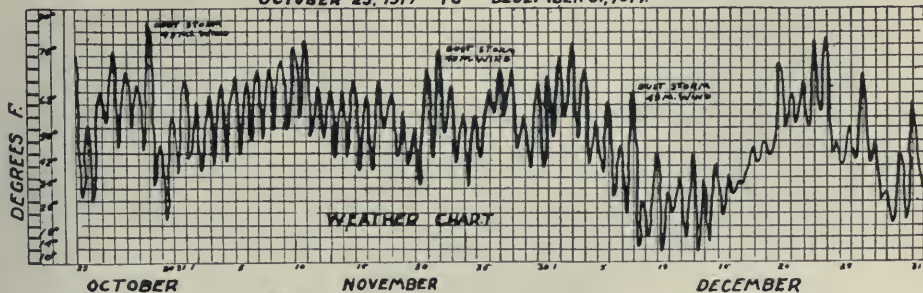
Examinations Made	Organisms Found	No. of Cases	Percentage of Cases
Dec. 6-15, 1917			
Sputum: 62 cases.....	Pneumococcus Type I.....	22	35.5
	Pneumococcus Type II.....	0	0
	Pneumococcus Type II atypical.....	9	14.5
	Pneumococcus Type III.....	2	3.2
	Pneumococcus Type IV.....	29	46.8
Pleural fluids: 17 cases...	Hemolytic streptococcus.....	13	76.0
	Pneumococcus Type II atypical.....	2	12.0
	Streptococcus viridans.....	2	12.0
Lung cultures: 30 cases...	Hemolytic streptococcus.....	18	60.0
Postmortem			
Dec. 15-31, 1917			
Sputum: 33 cases.....	Pneumococcus Type I.....	9	27.9
	Pneumococcus Type II.....	7	21.0
	Pneumococcus Type III.....	1	3.0
	Pneumococcus Group IV.....	13	39.0
	Pneumococcus Group IV and Hem. strep. ....	2	6.0
	Hemolytic streptococcus.....	1	3.0

*Bacteriology.*—The bacteriologic data included in this period were furnished by the Red Cross Laboratory Car "Metschnikoff," with Drs. Jobling and Maxwell and Captain Dochez, which was sent to this camp early in December, 1917, to assist the base hospital laboratory, at that time insufficiently equipped and manned to do the necessary work. After Dec. 15, 1917, the base hospital laboratory made routine type determinations by the glucose-blood-broth method (white mice were not available). The results of this work are shown in Table 1. The prevalence of infection with hemolytic streptococci is indicated by its high incidence in the pleural fluids and direct lung cultures.

#### PERIOD 2

During January and February, 1918, there was a large incidence of pneumonia, the clinical variety showing a greater percentage of lobar pneumonias and differing very little from the variety seen in civil life.

# DAILY INCIDENCE OF MEASLES AND PNEUMONIA OCTOBER 23, 1917 TO DECEMBER 31, 1917.



Type I pneumonia constituted 26.5 per cent. of the whole number. Between March 15 and April 15, 1918, 117 cases of pneumonia were admitted to the hospital, 10 of these (8.5 per cent.) showing *Streptococcus hemolyticus* in the sputum. The Type I cases dropped to 13.6 per cent. and Group IV pneumococcus showed 69.2 per cent.

Between March 26 and April 13, 349 cases of an acute respiratory infection were admitted. These were not called "influenza" because of lack of bacteriologic support for such a diagnosis. Clinically, they closely resembled the condition subsequently called influenza, although this diagnosis is questionable.

During the latter half of June, 1918, a large number of recruits in the Detention Camp developed severe bronchitis. Sputum from twenty of the more severe cases was submitted to the laboratory for examination. In addition, nasopharyngeal cultures were made from 60 contacts with these cases and from 60 men, chosen at random, throughout the camp.

*Method.*—Sputum: The sputum was washed three times in saline and emulsified in broth, then planted in dextrose-blood-broth. After six to eight hours' incubation, human blood-agar plates were streaked from these cultures and were studied after twelve to eighteen hours' incubation, and again after forty-eight hours' incubation. Pneumococcus colonies were fished into dextrose-blood-broth and pure cultures submitted to the test for bile solubility and agglutination with type serums. Colonies showing a wide area of hemolysis and having morphologic characteristics of streptococcus were considered hemolytic streptococcus.

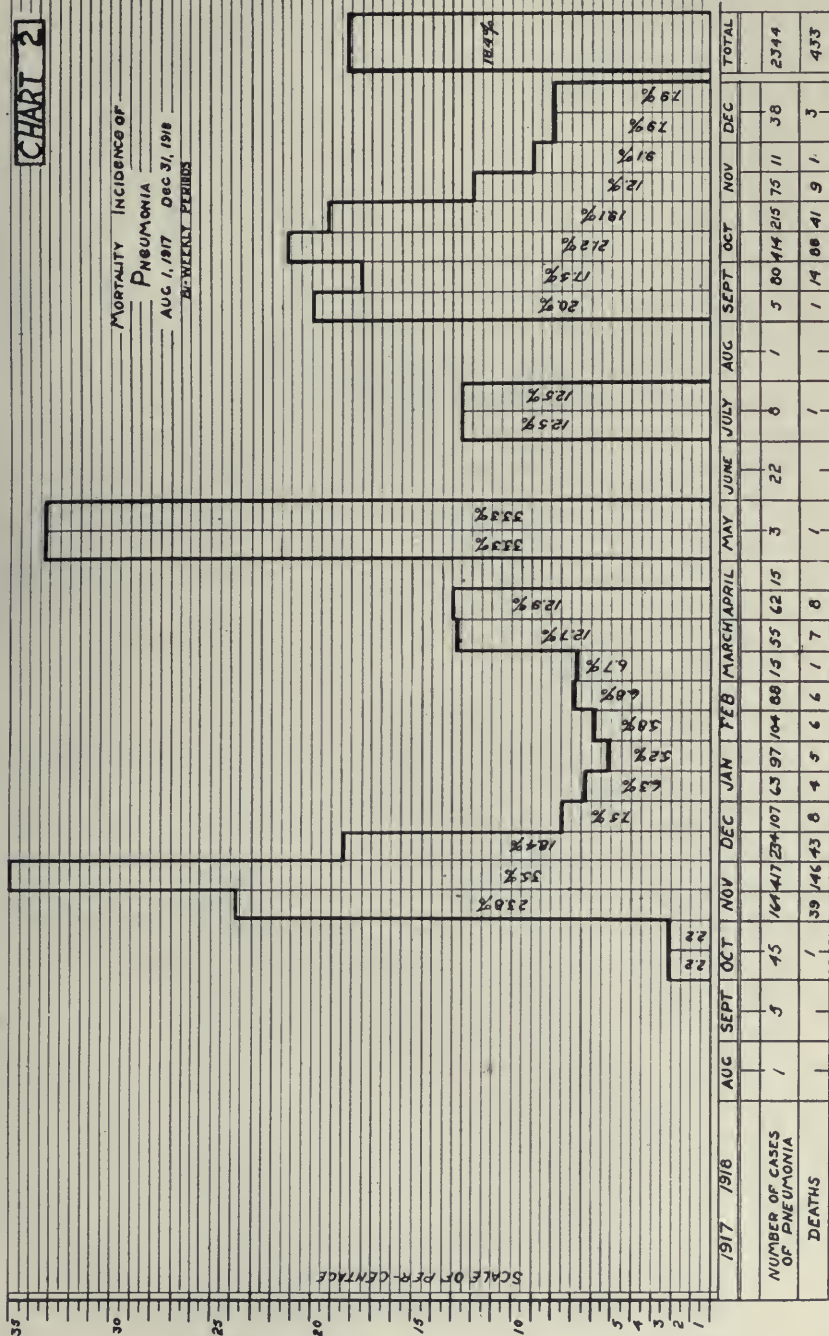
Naso-pharyngeal cultures: The naso-pharynx was swabbed as for meningococcus carrier detection. Swabs were placed immediately into plain broth tubes, and from these, human blood agar plates were streaked and incubated twenty-four to thirty-six hours. Plates were then studied for types of colonies. Organisms such as staphylococci and *Micrococcus catarrhalis* were not recorded. Results are given in Table 2.

TABLE 2.—ORGANISMS FOUND IN SPUTUM AND NASOPHARYNGEAL CULTURES FROM DETENTION CAMP AND FROM EQUAL NUMBER OF NORMAL CONTROLS (JUNE, 1918)

Organism Present	Sputum		Naso-Pharyngeal			
			Contacts		Controls	
	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.
Hemolytic streptococcus.....	20	100	..	...	..	...
Pneumococcus Type I.....	3	15	..	...	..	...
Pneumococcus Group IV.....	15	75	..	...	..	...
Hemolytic streptococcus, over.....	..	75	30	50	14	23.3
Pneumococcus undetermined, over.....	..	75	..	14	2	3.3
Pneumococcus and Hem. streptococcus..	..	...	8	13	3	5.0
Neither pneumococci nor streptococci....	..	...	20	33	44	75.0

CHART 2

MORTALITY INCIDENCE OF  
PNEUMONIA  
AUG 1, 1917 DEC 31, 1918  
2-WEEKLY PERIODS



During the remainder of Period 2, especially after the Thirty-Sixth Division left in July, there were only forty-three cases of pneumonia with two deaths. Nine of the forty-three showed the hemolytic streptococcus predominating in the sputum, and two were a mixed infection of hemolytic streptococcus and Group IV pneumococcus.

Of the 538 pneumonia patients, only forty-eight gave a history of an antecedent infection within a month. In the great majority of instances there was a definite history of exposure, insufficient clothing, or overheating, followed by injudicious cooling, which may have been the precipitating factor in the onset.

The total mortality for this period was 7.4 per cent., there being forty fatalities among the 538 cases. Fifty-two patients (9.7 per cent.) developed empyema and provided 37.5 per cent. of the total deaths.

*Bacteriology.*—It is significant that in all the lobar pneumonia cases pneumococci were found in the sputum, and ten of the eighteen fatal cases reacted to specific type serums I and II. Hemolytic streptococci were still an important factor (Table 2), and in three of nine purulent pleurisies this organism was present in addition to the pneumococcus. During the month of April there occurred four cases of interstitial bronchopneumonia caused by the hemolytic streptococcus. These cases occurred at the time of the small epidemic of acute respiratory infection previously described.

#### PERIOD 3

*Influenza.*—The development of the epidemic on September 17 began with the admission of cases of a not uncommon type of upper respiratory tract infection, numbering about five daily, before the semblance of an epidemic was evident. On September 26, twenty-four cases of influenza were admitted. During the epidemic which continued to Nov. 15, 1918, 3,876 cases of this infection were admitted to the base hospital. Six hundred and thirty-four cases were held in the observation wards of the Detention Camp.

*Blood Counts.*—Study of the table of blood counts (Table 3) in uncomplicated influenza shows that during the first five weeks, representing the period of highest incidence, the largest number of counts were below 10,000; the polynuclear percentage was below seventy, and the lymphocyte percentage was over twenty-five. As the severity of the epidemic declined, the total white counts were higher, and the polynuclear percentages were correspondingly increased. The same transition is apparent in the pneumonia following influenza (Table 10), although the percentage of high counts is greater than in the uncomplicated cases.

# DAILY INCIDENCE - INFLUENZA & PNEUMONIA SEPTEMBER 25, 1918 - DECEMBER 31, 1918

CHART 3

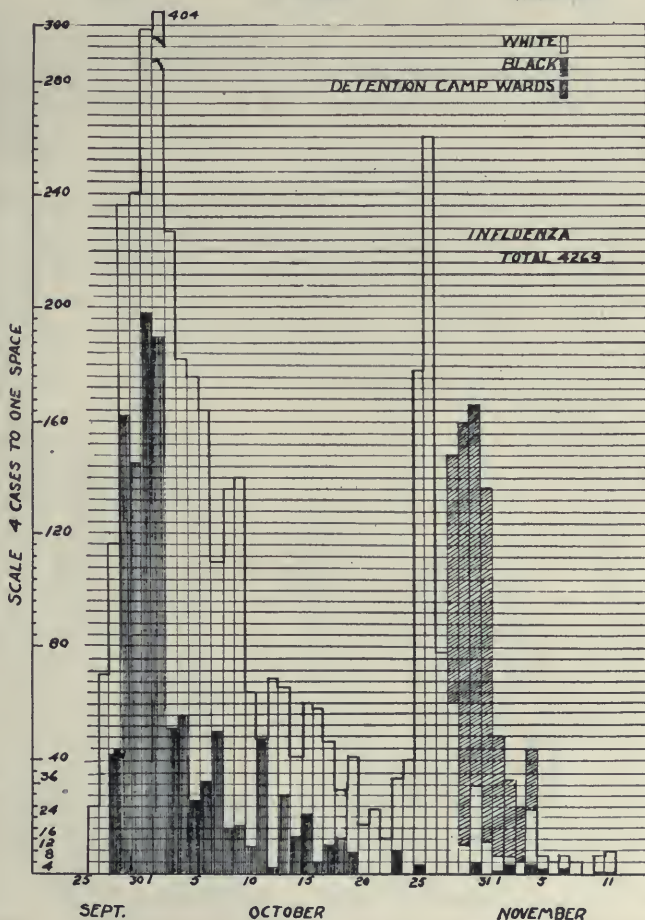
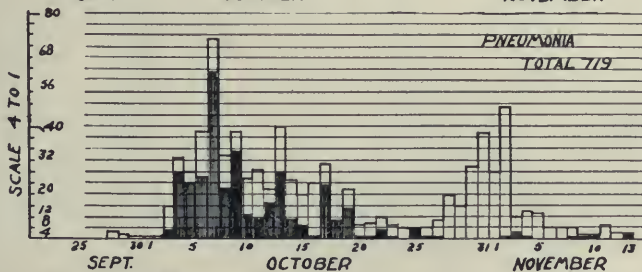
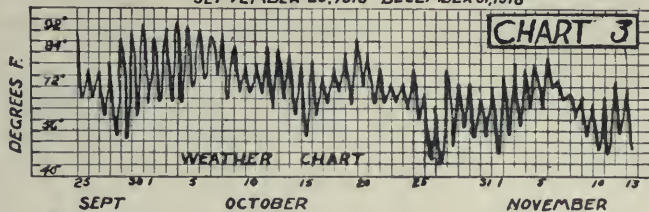


TABLE 3.—BLOOD COUNTS IN UNCOMPLICATED INFLUENZA CASES (BASED ON 400 COUNTS MADE DURING THE FIRST FIVE DAYS OF THE DISEASE)

	Sept. 25-30, 1918		Oct. 1-31, 1918		Nov. 1-30, 1918	
	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.
Total counts.....	49	....	212	....	139	....
Under 5,000.....	...	....	8	3.0	1	1.0
5,000-10,000.....	37	76.0	138	65.0	33	23.5
Over 10,000.....	12	24.0	66	32.0	105	75.5
Differential counts.....	29	....	155	....	126	....
Polymorphonuclear neutrophils						
Under 50 per cent. ....	1	3.5	3	2.0	...	....
50-70 per cent. ....	15	51.5	67	43.0	43	34.5
71-85 per cent. ....	12	41.5	83	53.5	82	65.0
Over 85 per cent. ....	1	3.5	2	1.5	1	0.5
Lymphocytes						
10-25 per cent. ....	9	31.0	67	43.5	79	62.5
25-50 per cent. ....	20	69.0	85	54.5	47	37.5
Over 50 per cent. ....	...	....	3	2.0	...	....

Leukopenia (counts under 5,000) was not a common finding, though absence of leukocytosis was the rule.

This change in the blood findings was synchronous with a somewhat changed clinical picture. The epidemic reached its peak in numbers in seven days, and at the end of the second week the severity of the infection was decreasing, as shown by a less profound prostration, diminished general malaise, less frequent and milder toxic erythema and more rapid convalescence.

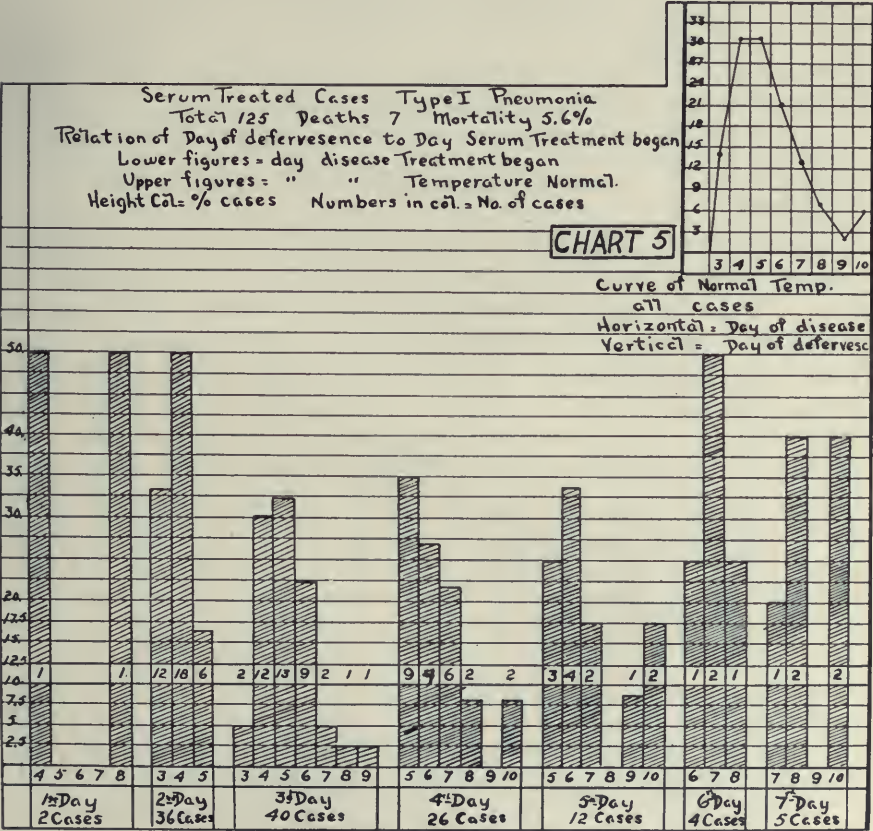
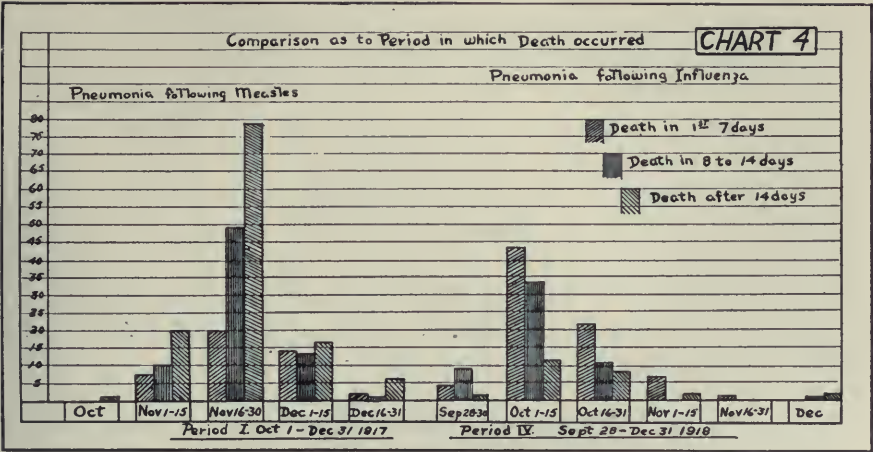
Reference to Chart 3 shows that the first peak of the influenza precedes that of the pneumonia by five days. The second peak, occurring three weeks later, coincident with the arrival of the first increment of drafted troops from Missouri, precedes the second peak of the pneumonia by seven days. There were received at the detention camp during the course of the epidemic 4,108 drafted white men and 2,360 drafted colored men.

Among the white men, 252 per thousand men who were exposed developed the infection, 114 per thousand developed pneumonia. Not every pneumonia patient gave a history of an antecedent influenza infection. Among the 795 cases of pneumonia, a history of influenza within the preceding month was obtained in 728.

No deaths were attributable to uncomplicated influenza. The total deaths in the 833 cases of pneumonia, numbered 156, a mortality of 18.7 per cent. Thirty-six men (4.3 per cent.) developed empyema and furnished 11.5 per cent. of the total deaths.

It is interesting that in spite of the higher morbidity rate for influenza and pneumonia among black troops, the mortality percentage (17.1 per cent.) among them was somewhat less than that of the white troops (20.8 per cent.).

From Chart 2 it would at first appear that the highest mortality was reached quickly after the onset of the epidemic, the virulence of the infection decreasing thereafter and the mortality diminishing from



21.2 and 19.1 per cent. to 12 and 9.1 per cent., respectively, for semi-monthly periods. That this may have been partly true is evidenced by the fact that the patients admitted after the first two weeks did not appear to be so severely ill. That the virulence of the infecting organism persisted is shown by the incidence and mortality of pneumonia among the Missouri drafted men, who arrived three weeks after the peak of the epidemic was reached. These men arrived in camp from October 22 to October 25. They were overtaken by influenza October 23-31 and developed pneumonia October 28 to November 4. Among them there developed 199 cases of pneumonia with thirty-nine deaths, a mortality (19.6 per cent.) almost equal to that occurring at the height of the epidemic. The lower total mortality for the first half of November was due to the inclusion of ninety-one scattered cases occurring among troops that had been in camp longer. Among these cases there were only eleven deaths, a mortality of 12 per cent.

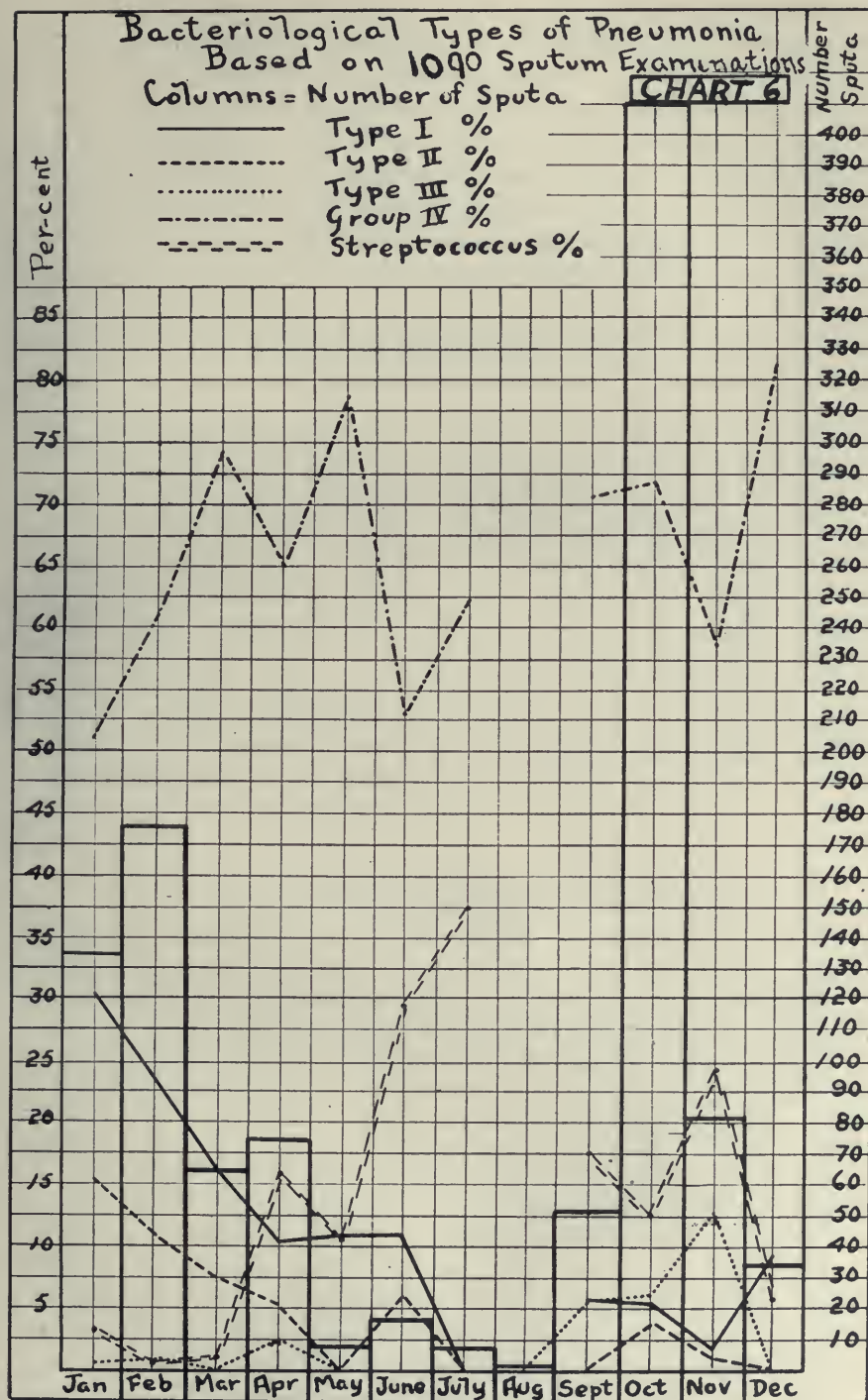
*Bacteriology.*—Sept. 25, 1918, routine naso-pharyngeal swabs were made in all cases admitted with the diagnosis of influenza. In all, seventy-five cases were examined satisfactorily.

*Method:* Swabs were made from the naso-pharynx as described in "Standard Method for Meningococcus Carriers for U. S. Army." These were first streaked on human blood-agar plates, and afterward immersed in glucose-blood-broth. The latter cultures were incubated about six hours and human blood-agar plates were then streaked from them.

*Identification:* Streptococci and pneumococci by "Standard Method for U. S. Army," except that press of other work prevented identification of types of pneumococci. Plates were incubated eighteen to twenty-four hours. Influenza bacilli when found in quantity were present in characteristic growth in this time. The results are shown in Table 4.

TABLE 4.—BACTERIOLOGY OF NASO-PHARYNGEAL CULTURES IN INFLUENZA

	Number	Per Cent
Hemolytic streptococci (colonies over 75 per cent.).....	34	45
Associated organisms:		
Pneumococci (type undetermined).....	18	
Staphylococci.....	19	
Unidentified Gram positive bacilli.....	3	
Pneumococci, type undetermined (colonies over 75 per cent.).....	26	35
Associated organisms:		
Hemolytic streptococci.....	7	
Nonhemolytic streptococci.....	2	
Staphylococci.....	11	
Micrococcus catarrhalls.....	1	
Influenza bacilli present.....	7	9
Associated organisms:		
Hemolytic streptococci.....	3	
Pneumococci (type undetermined).....	2	
Micrococcus catarrhalls.....	2	
Staphylococci.....	4	
Nonhemolytic streptococci (colonies over 75 per cent.).....	8	10
Associated organisms:		
Staphylococci.....	6	
Micrococcus catarrhalls.....	2	
Friedländer bacilli.....	1	



Postmortem Bacteriology: The bacteriology during Period 3, as determined by lung cultures and the incidence of complications in the three types of cases, (1) lobar pneumonia, (2) bronchopneumonia of the confluent lobular type, and (3) bronchopneumonia of the interstitial type, is shown in Tables 5, 6 and 7. The group showing the interstitial type of pneumonia and the highest proportion of complications, showed hemolytic streptococcus in 64 per cent. of lung cultures, just as our experience with streptococcus pneumonia complicating measles had led us to expect.

TABLE 5.—BACTERIOLOGY OF LOBAR PNEUMONIA (TWENTY-FOUR CASES) AS DETERMINED BY LUNG CULTURES

	Cases
Not examined .....	8
Pneumococcus, Type II, alone.....	1
Pneumococcus, Group IV, alone.....	7
Pneumococcus, Group IV and influenza.....	2
Pneumococcus, Group IV, influenza and nonhemolytic streptococcus.....	1
Pneumococcus, type undetermined, alone.....	3
Pneumococcus, type undetermined and influenza.....	1
Pneumococcus, type undetermined and Micrococcus catarrhalis.....	1
Influenza bacillus, 4 cases; 25 per cent.	
Complications	Per Cent.
Pleurisy, purulent .....	12.5
Pleurisy, fibrinous .....	30.0
Pleurisy, serofibrinous .....	12.5
Pleurisy, serous .....	8.0
Meningitis, purulent .....	12.5
Substernal pus pocket .....	4.0
Lung abscess .....	4.0
Peritonitis, purulent .....	4.0
Edema, brain .....	4.0
Average duration of disease 9.2 days.	

TABLE 6.—BACTERIOLOGY OF BRONCHOPNEUMONIA—CONFLUENT LOBULAR TYPE (68 CASES)

	Cases
Not examined .....	17
Pneumococcus, type undetermined, alone.....	10
Pneumococcus, type undetermined and influenza.....	5
Pneumococcus, type undetermined and Micrococcus catarrhalis.....	1
Pneumococcus, Group IV, alone.....	14
Pneumococcus, Group IV and influenza.....	1
Pneumococcus, Type III, alone.....	1
Pneumococcus, Type I, alone.....	1
Influenza and M. catarrhalis.....	2
Hemolytic streptococcus, alone .....	1
Hemolytic streptococcus and pneumococcus, Group IV.....	11
Nonhemolytic streptococcus, alone .....	1
Nonhemolytic streptococcus and influenza.....	1
Bacillus of Friedländer, alone.....	1
Hemolytic streptococcus, 3 cases; 6 per cent.	
Influenza bacillus, 8 cases; 16 per cent.	
Complications	Per Cent.
Pleurisy, purulent .....	4.5
Pleurisy, serofibrinous .....	11.0
Pleurisy, fibrinous .....	23.0
Pleurisy, serous .....	4.5
Pericarditis, serofibrinous and purulent.....	3.0
Metastatic abscess .....	3.0
Average duration of disease 8.5 days.	

Influenza bacilli were found in 16 per cent. of the remaining bronchopneumonias and in 25 per cent. of the lobar pneumonias, and always associated with other organisms.

In all of the lobar pneumonia cases the pneumococcus was found. In the bronchopneumonia cases of the confluent lobular type, thirty-five (70 per cent.) yielded pneumococcus Group IV pneumococcus, type undetermined, or nonhemolytic streptococcus.

Satisfactory cultures were made postmortem from heart's blood in eighty-one cases, with results as shown in Table 8.

TABLE 7.—BACTERIOLOGY OF BRONCHOPNEUMONIA—INTERSTITIAL TYPE  
(33 CASES)

	Cases
Not examined .....	11
Streptococcus, hemolytic, alone .....	10
Streptococcus, hemolytic and pneumococcus, Group IV.....	1
Streptococcus, hemolytic and pneumococcus, undetermined.....	2
Streptococcus, hemolytic and influenza.....	1
Streptococcus, nonhemolytic, alone .....	1
Streptococcus, nonhemolytic and influenza.....	1
Pneumococcus, undetermined, alone .....	1
Pneumococcus, undetermined and Friedländer bacillus.....	1
Pneumococcus, Type III, alone.....	1
Pneumococcus, Group IV, alone.....	3
Streptococcus, hemolytic, 14 cases; 64 per cent.	
Influenza bacillus, 2 cases; 9 per cent.	
Complications	Per Cent.
Pleurisy, purulent .....	40
Pleurisy, serofibrinous .....	18
Pleurisy, fibrinous .....	28
Pericarditis, serofibrinous and purulent.....	9
Peritonitis, purulent .....	9
Substernal pus pocket.....	9
Metastatic abscess .....	3
Lung abscess .....	6
Average duration of disease 14.5 days.	

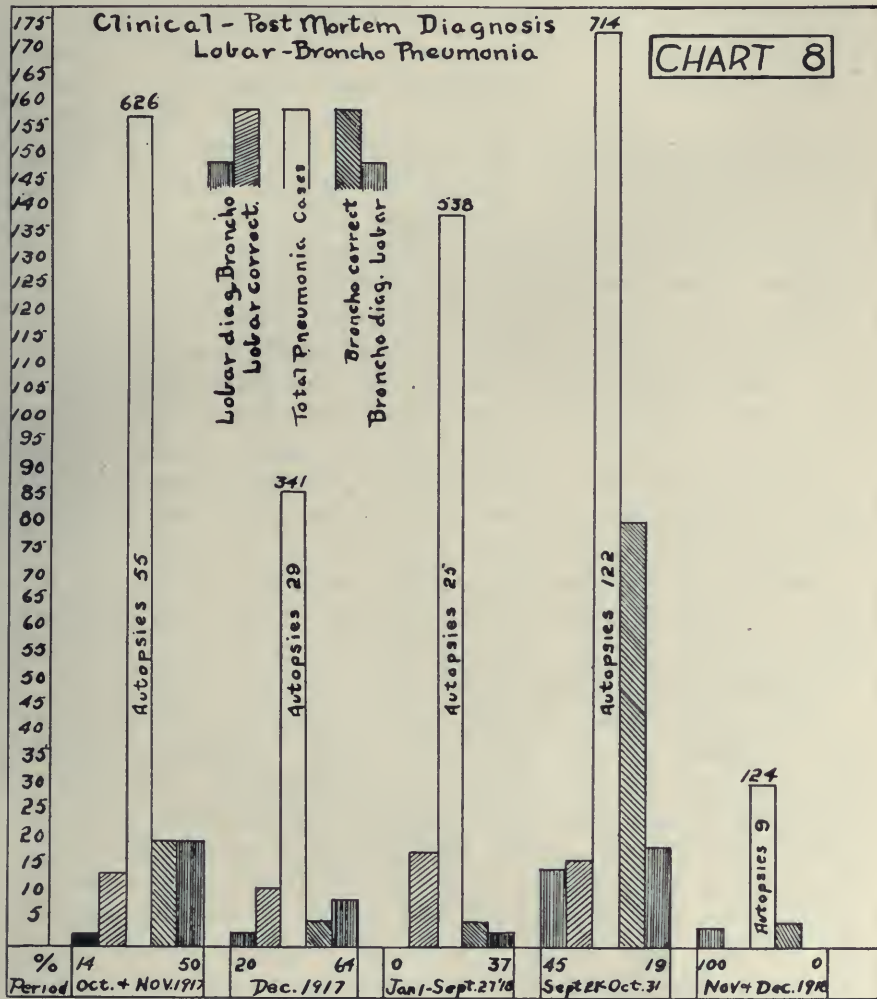
TABLE 8.—BACTERIOLOGY OF CULTURES FROM HEART'S BLOOD  
(POSTMORTEM)

Total cultures .....	81
No growth .....	19
Pneumococcus, type undetermined.....	19
Pneumococcus, Group IV.....	17
Pneumococcus, Type I.....	1
Pneumococcus, Type II.....	2
Pneumococcus, Type III.....	1
Streptococcus, hemolytic .....	11
Streptococcus, nonhemolytic.....	11

*Diagnosis.*—Certain cases, especially cases of lobar pneumonia, have offered no difficulty in diagnosis. In the secondary pneumonias, those following measles in 1917, and especially those following influenza in 1918, it was the rule rather than the exception for the signs to be so irregular as to offer the greatest difficulty in diagnosis, not only as to the evidence of consolidation, but especially as to the clinical variety. The sputums from these cases have practically all shown streptococcus, pneumococcus Group IV, or a mixed infection.



In September and October, 1918, during the influenza epidemic, there were 714 cases of pneumonia, of which 122 came to necropsy. Of these 122 cases, eighteen were diagnosed correctly lobar pneumonia, fifteen were wrongly called bronchopneumonia (45 per cent.). Eighty-one cases were properly diagnosed as bronchopneumonia; nine-



teen cases were wrongly called lobar pneumonia (19 per cent.). There were certain extenuating circumstances for these wrong diagnoses. Even at the postmortem table the differentiation was frequently puzzling. The fact remains that statistics based on clinical differentiation between lobar and bronchopneumonia seen at this hospital during the first sixteen months of its existence are not reliable. For this

reason we have not included the differentiation in the tables and charts, except in Chart 7, which will serve as a comparison with figures furnished from other sources.

*Onset.*—As this was observed in the pneumonias following measles and in those following influenza, there was a great difference in the two epidemics. In 1917 it apparently took longer for an acute infection of the upper respiratory tract to develop into a pneumonia. A history of an acute infection existing several weeks before the pneumonia developed was often obtained. In the post-influenzal pneumonias, the signs of consolidation rarely appeared later than five days after the initial symptoms of the influenza; the duration of the febrile period of influenza having been two to five days, most often three. The infections following both epidemics were usually of the descending type. In some cases the involvement of the lungs and pleura appeared almost simultaneously, leaving it doubtful whether the consolidation or the empyema came first. In 1917, especially, the pleural involvement was often the initial and outstanding feature; the pain was intense, the prostration extreme, the face flushed, the features drawn and fluid (usually streptococcal) formed before signs of consolidation were manifest. In the majority of cases pain and chill did not figure in the onset. The increased temperature, high pulse and increased respiratory rate were indications for careful and frequently repeated physical examinations.

During periods 1 and 2 cases were seen occasionally in which the signs of meningitis ushered in the infection. Usually, the meningeal signs persisted for about twenty-four hours; then the first signs of consolidation would appear. Spinal fluids were negative.

*Signs.*—The physical signs in the majority of these difficult cases were extremely irregular and rarely frank. Dulness, suppressed breath sounds, often moist crackling râles, especially at the height of inspiration, or even a change in the quality of the breath and voice sounds—one or more of these, but rarely all, were the bases of the diagnosis. In the absence of supporting evidence—such as the subsequent course of the disease, leukocyte counts and roentgenograms—many of these cases would not have been diagnosed. It was not an infrequent experience to have the frank signs follow several days after the decline of temperature and improvement in the general condition.

*Lobes Involved.*—Of 1,533 cases in which the first involvement noted affected only one lobe, the right lower lobe was involved first in 711 cases, the left lower lobe in 679 cases, the right upper lobe in 54 cases, the left upper lobe in 48 cases, and the right middle lobe in 41 cases. In a large number of the cases of pneumonia associated with

the influenza epidemic, the initial involvement was simultaneous in both lower lobes. It is of anatomic interest to note that in four necropsies an additional lobe was observed twice on the left and twice on the right side.

*Blood Counts.*—In Periods 1 and 2 the blood counts were such as are ordinarily encountered in pneumonia. During the first five days of the disease about 85 per cent. of the total number of white counts made was over 10,000, and in the same proportion of cases the polynuclear percentage was 70 or over (Table 9).

TABLE 9.—BLOOD COUNTS IN PNEUMONIA

	Period 1 Sept. 25- Dec. 31,		Period 2 Jan. 1- Sept. 27,		Period 2—Following Influenza					
	Cases	Per Cent.	Cases	Per Cent.	Sept. 28-30,		Oct. 1-31,		Nov. 1-30,	
					Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.
Total Counts:										
During first five days—										
Under 5,000.....	1	2	2	4	3	10	10	8	..	..
5,000-10,000.....	4	8	6	12	12	38	79	60	7	30
Over 10,000.....	45	90	43	84	16	51	41	31	16	70
After five days—										
5,000-10,000.....	4	19	1	14	6	43	24	30	..	..
Over 10,000.....	18	81	6	86	8	57	57	70	3	100
	72		58		45		211		26	
Differential Counts:										
Polymorphonuclears—										
50-70 per cent. ....	7	10	2	5	6	25	42	43	2	8
70-85 per cent. ....	43	64	24	53	17	75	53	54	19	83
Over 85 per cent. ....	17	25	19	42	..	..	3	3	2	8
	67		45		23		98		23	

When the figures for these two periods are compared with those for Period 3, it will be noted that they are very nearly reversed—60 per cent. of these counts being *under* 10,000, while in 35 per cent. the polynuclear percentage was below seventy.

It is not unreasonable to infer that the failure of the individual to react to his pneumonia with a leukocytosis at this time is evidence of a diminished resistance produced by the preceding influenza. In this connection it is interesting to note that of thirty-one counts made in cases in which no antecedent history of influenza was present during Period 3, twenty-seven were over 10,000 (average 15,000) and only four were below 10,000. Also that the average duration of illness in fatal cases during the first two periods was twenty-one days, while in the last period it was eleven days.

*Blood Cultures.*—Of 254 satisfactory blood cultures taken during life, thirty-five, or 13.8 per cent. were positive. Of the 219 cases in which sterile blood cultures were obtained, twenty-four, or 11 per cent., of the patients died, whereas of the thirty-five cases with positive blood

cultures fourteen patients, or 40 per cent., died. This is in accord with the view that a positive blood culture during life makes the prognosis grave.

*Bacteriological Examination of Sputum.*—Chart 6 shows type determinations for the year 1918. Of the 1,371 cases of pneumonia occurring in 1918, the sputum in 1,090, or 79.5 per cent., was typed. From Dec. 28, 1917, to Jan. 20, 1918, Type III serum was not obtainable; therefore, Group IV for this period may include some Type III cases. During the four winter months—December, January, February and March—the percentage of incidence of Type I was 23.8. The incidence during the period of good weather was 5.9 per cent. With Type II the winter months showed an incidence of 11.1 per cent.—the summer months 3.1 per cent. In contrast to the decreased incidence of these fixed types, Group IV pneumococcus shows 61.9 per cent. in the winter months and 69.2 per cent. in the summer months. The streptococcus curve includes both hemolytic and non-hemolytic streptococci, and resembles the Group IV curve in its variations.

TABLE 10.—PNEUMONIA: CASES AND MORTALITY ON THE BASIS OF 1,090 SPUTUM TYPE DETERMINATIONS

	Cases	Deaths	Mortality, per Cent.
Pneumococcus Type I.....	142	7	4.9
Pneumococcus Type II.....	68	14	20.6
Pneumococcus Type III.....	45	6	13.3
Pneumococcus Group IV.....	722	75	10.4
Pneumococcus Group IV and Hemolytic strep. ....	25	6	24.0
Nonhemolytic streptococcus.....	5	5	100.0
Hemolytic streptococcus.....	83	11	13.3

The mortality in the various types of infecting organisms, as determined by sputum examinations, is shown in Tables 10 and 11. It is interesting to note the variations in mortality for the same type in different periods. All types, with the exception of Type III, showed a much higher mortality during Period 3 (accompanying the influenza epidemic) than they had shown during the first nine months of the year.

TABLE 11.—PERIODS 2 AND 3. MORTALITY OF VARIOUS TYPES OF ORGANISMS COMPARED

	Mortality Percentage, Jan.-Sept.	Mortality Percentage, Oct.-Dec.
Pneumococcus Type I.....	4.3	7.4
Pneumococcus Type II.....	15.0	37.5
Pneumococcus Type III.....	20.0	12.5
Pneumococcus Group IV.....	7.6	12.0
Streptococcus—hemolytic and nonhemolytic.....	7.4	23.0

Experience at this hospital has shown that to limit the investigation of sputum to a determination of the type of pneumococcus present,

does not always give a reliable guide as to the nature of the existing infection. We need only call attention to a comparison of our sputum type determination, with the bacteriology found in pleural fluids and at necropsy, during Period 1 (Table 1) to illustrate this point. It seems necessary to attempt to determine the predominating organisms. Our practice has been to estimate this from a differential count of colonies on human blood-agar plate streaked from either first culture in glucose-blood-broth or from the peritoneal cavity of the mouse.

Comparing the findings in the sputum with the other bacteriologic findings in the same case, such as from the examination of blood cultures, pleural fluids, lung cultures, necropsy, etc., should furnish the best evidence as to their value in ordinary hospital practice. Such a comparison is made in Table 12. The percentage of correspondence is high, taking into consideration the conditions under which the work was done, and indicate that this procedure should remain one of our routine diagnostic methods for the study of pneumonia.

TABLE 12.—COMPARISON OF SPUTUM WITH OTHER BACTERIOLOGIC FINDINGS

Sputum	With Other Bac- teriologic Findings	Corre- sponding	Per Cent.	Dif- ferent	Per Cent.
Pneumococcus Type I.....	7	5	71	2	29
Pneumococcus Type II.....	12	6	50	6	50
Pneumococcus Type III.....	6	1	16	5	84
Pneumococcus Group IV.....	74	40	54	34	46
Streptococcus, hemolytic.....	17	13	76	4	24
Streptococcus, nonhemolytic.....	4	3	75	1	25

*Course.*—The progression toward a fatal termination varied considerably in those cases occurring in the fall of 1917, as contrasted with those in the fall of 1918. In the former period an extreme cyanosis, hoarse, barking cough, anxious facies, with all the accessory muscles of respiration in use, presented a fearful picture of what seemed the horror of death. In 1918, there was comparatively little of this. Even in the streptococcus infections death was preceded by a much more quiet period. This was especially true in the case of the negroes (there were none in camp in 1917). They usually remained quiet with shallow respirations, and met death quietly.

Chart 4 shows the deaths occurring in the two epidemic periods with reference to the duration of the illness. Accompanying the measles epidemic it is always an increasing number for the first week, the second week and after the second week. During the influenza epidemic the number dying in the first week is greater than that in the second week, and the least number survive more than 14 days.

## TREATMENT OF PNEUMONIA

*Serum Therapy.*—The specific serum has been used in all Type I cases, except those which had practically defervesced at the time of type determination.

The time between sending the sputum to the laboratory and the giving of the serum was eight to twelve hours, except during the epidemic, when the stress of work prevented the desensitizing of all pneumonia patients as soon as the diagnosis was made.

There were during 1918, 142 Type I infections. One hundred and twenty-five patients were treated with serum; seven died—a mortality of 5.6 per cent. (Table 13). Four of these seven deaths, while charged to pneumonia, really were caused by empyema, twenty-nine, twenty-eight, twenty-four and fifteen days, respectively, after the development of the pneumonia. Eliminating these deaths, the mortality of the treated cases would be 2.4 per cent.

TABLE 13.—COMPLICATIONS

	Total Cases	Cases Recognized Only at Necropsy	Per Cent. Recognized Only at Necropsy
Empyema.....	249	28	11
Pleurisy with effusion.....	101	38	38
Otitis media—suppurative (22 bilateral).....	105		
Otitis media—catarrhal (13 bilateral).....	40		
Mastoiditis (2 bilateral).....	25	3	12
Pericarditis.....	24	15	58
Metastatic abscess.....	17	3	18
Emphysema, subcutaneous, generalized.....	8		
Emphysema, mediastinal tissues only.....	10	10	100
Lung abscess.....	9	6	67
Meningitis.....	12	2	17
Peritonitis.....	12	8	67
Substernal pus pockets.....	7	7	100
Thrombophlebitis.....	8		
Nephritis, chronic parenchymatous.....	1		
Nephritis, acute toxic.....	18	18	100
Sinusitis.....	5		
Myocarditis.....	1		
Toxic psychosis.....	1		

Seventeen Type I infections were untreated. None of these patients died. The untreated patients were for the most part those who, because of the mildness of their infection, or delay in being sent into the hospital, had their crisis before the type of the infection could be determined. A few of these patients were sensitive to horse serum, but were not treated because they were not very sick.

No serious results have followed the administration of serum, and we feel that our experience is a strong argument for its use. The earlier it is used, the more striking are the results obtained. This is shown in Chart 5, which gives the relation of the day of defervescence to the day on which serum treatment was begun.

*Digitalis*.—All patients received digitalis in large doses as soon as the diagnosis was made. In Period 3, when a standardized tincture was obtained, it was administered in therapeutic dosage.

*General Measures*.—Treatment other than that already referred to was symptomatic.

*Gross Pathology*.—Period 1: The first cases coming to necropsy in November, 1917, showed the well known, typical lesions of acute lobar pneumonia. Of the first eight cases two showed pleural effusions—one serofibrinous and the other purulent.

TABLE 14.—RELATION OF PLEURAL EXUDATE AND SPUTUM IN SIXTY-EIGHT CASES OF EMPYEMA

	Cases	Deaths	Percentage of Mortality
1. Pneumococcus in both sputum and pleural fluid.....	32	6	19
2. Hemolytic streptococcus in both sputum and pleural exudate.....	3	1	33
3. Pneumococcus and hemolytic streptococcus in both sputum and pleural exudate.....	30	10	33
4. Sterile empyemas, pneumococcus in sputum.....	3	0	0
Total.....	68	17	25

As measles became more prevalent, and as both the incidence and mortality of pneumonia rose, the picture changed. More lobes were involved. Instead of feeling uniformly firm and airless, the affected tissue felt nodular, or "shotty," and distinct crepitation could be elicited between the firm nodules. Fibrinous deposits over the pleural surface were more constant and more extensive. On section, the cut surface of lung presented a mottled appearance, usually a dark, bluish-red background, with many small slightly elevated grayish red areas, each presenting the opening of a bronchiole, at or near its center. In many cases these areas were confluent. The interlobular septums were distinctly visible, dividing the lobe into a number of irregularly shaped areas. Abscess formation, especially multiple small abscesses, was occasionally found.

Effusions into the pleural cavity became increasingly frequent, and were usually purulent. Adhesions between the visceral and parietal pleura occurred, often dividing the pleural cavity into two or more distinct compartments. Perhaps, the most frequent site of such adhesion was between the anterior edge of the lung and the costal margin, the inner surface of the sternum or pericardial sac. Here elongated pockets were formed, at times divided by transverse bands into two, which contained thick greenish pus and masses of fibrin. Adhesions between the lobes with formation of interlobular abscesses were also found.

The pericardium was involved in many cases. In some instances only the external surface showed a fibrin deposit of varying thickness with organization, and adhesion to sternum, ribs and left lung. In other instances, the inner surface was dull, covered with a rough fibrin deposit, and the sac contained a large amount of serofibrinous or purulent fluid, in which hemolytic streptococci were found.

TABLE 15.—PROCEDURE IN EMPYEMA

Method of Treatment	Aspiration No.	Period 1		Period 2		Period 3		Total Cases	Mortality per Cent.
		Cases	Deaths	Cases	Deaths	Cases	Deaths		
Aspiration alone	1	21	20	..	..	2	2	23	84
	2	4	3	1	1	2	1	7	71
	3	3	2	1	1	1	0	4	75
	8	..	..	..	..	1	0	1	0
Costatectomy preceded by aspiration	1	89	26	27	5	5	1	121	26
	2	10	2	8	0	2	0	20	10
	3	4	0	6	1	..	..	10	10
	4	2	1	1	0	1	0	4	0
	5	..	..	..	..	1	0	1	0
	7	1	1	..	..	1	0	2	0
	9	..	..	1	0	..	..	1	0
	10	..	..	..	..	1	0	1	22
Thoraeotomy preceded by aspiration	1	11	7	..	..	1	0	12	58
	2	3	3	..	..	2	0	5	60
	3	1	1	1	1	2	1	4	75
	4	..	..	..	..	1	1	1	100
	5	..	..	..	..	1	1	1	100

## SUMMARY

	Costatectomy			Thoraeotomy			Aspiration			Total		
	Cases	Deaths	Mortality per Cent.	Cases	Deaths	Mortality per Cent.	Cases	Deaths	Mortality per Cent.	Cases	Deaths	Mortality per Cent.
Period 1* Oct. 1- Dec. 31, 1917	106	30	28.3	15	11	73	29	26	89	150	67	44.6
Period 2 Jan. 1- Sept. 27, 1918	43	6	14.0	7	1	100	3	3	100	47	10	21.3
Period 3 Sept. 27- Dec. 31, 1918	11	1	9.0	1	3	43	6	2	33	24	6	25.0
Total	160	37	....	23	15	....	38	31	....	221	83	37.5

\* Two cases (2 deaths) included in totals for aspiration only had no aspiration before death.

*Microscopic.*—The microscopic picture in these cases was that described by MacCallum<sup>1</sup> as interstitial pneumonia. The illustrations

1. Cole R., and MacCallum, W. G.: Pneumonia at a Base Hospital, J. A. M. A. **70**:1147, 1918.

show some of the constant findings — peribronchial consolidation, involvement of interstitial tissue, and extensive fibrino-purulent pleurisy.

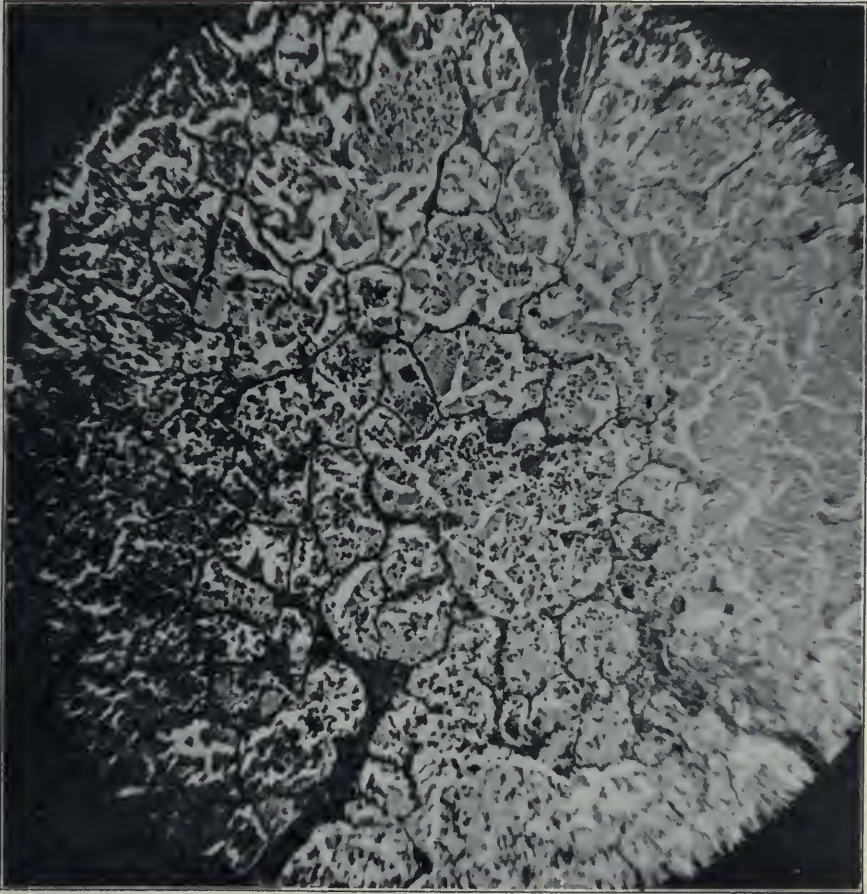


Fig. 1.—Section of lung affected with a confluent lobular bronchopneumonia following influenza. Early exudate.

#### PERIOD 2

Of twenty-five postmortems, lobar pneumonia was found in nineteen cases; bronchopneumonia, of the interstitial type, was found in six cases. The incidence of purulent pleurisy was high (50 per cent.). This may be explained by the fact that five of the six bronchopneumonia cases showed this complication, and hemolytic streptococci were found as complicating organisms in one-third of the cases following pneumococcus infection.

## PERIOD 3

*Gross Pathology.*—Three distinct types of cases were found: (1) lobar pneumonia; (2) bronchopneumonia of interstitial type, the lesions of which have just been described, and (3) bronchopneumonia of a lobular or confluent type.

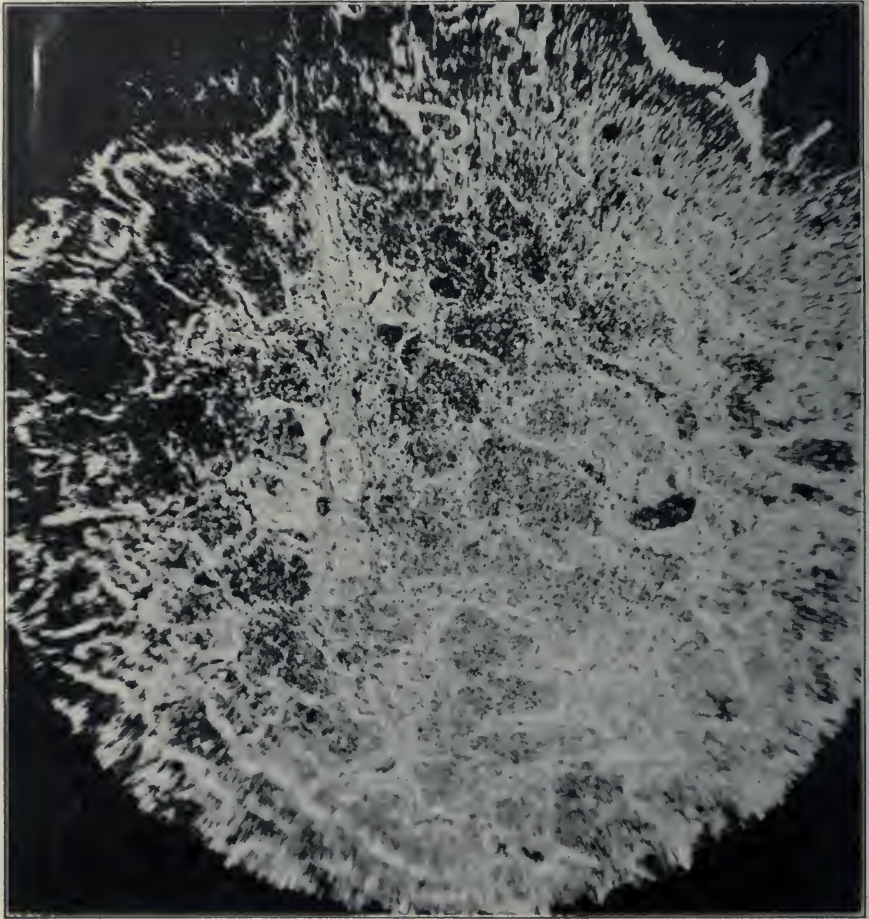


Fig. 2.—Section of lung affected with a confluent lobular bronchopneumonia following influenza. Later exudate.

In the latter cases, the lungs were large, moderately firm, all more or less nodular. Frequently, by careful palpation, crepitating areas could be felt, even in a lobe which was apparently completely consolidated. The pleural covering was usually smooth and transparent, many cases showing scattered small areas of subpleural hemorrhage. Fine fibrinous deposits were found in some cases very early in the course of the

pneumonia. In those cases which showed emphysema of the mediastinal tissues there was usually an emphysema just beneath the pleura which extended mainly along the interlobular septa.

Section of the lung was followed by the outpouring of a large amount of dark, bloody fluid. The cut surface was dark, bluish red, mottled with lighter areas, which varied in color from a deep brownish-

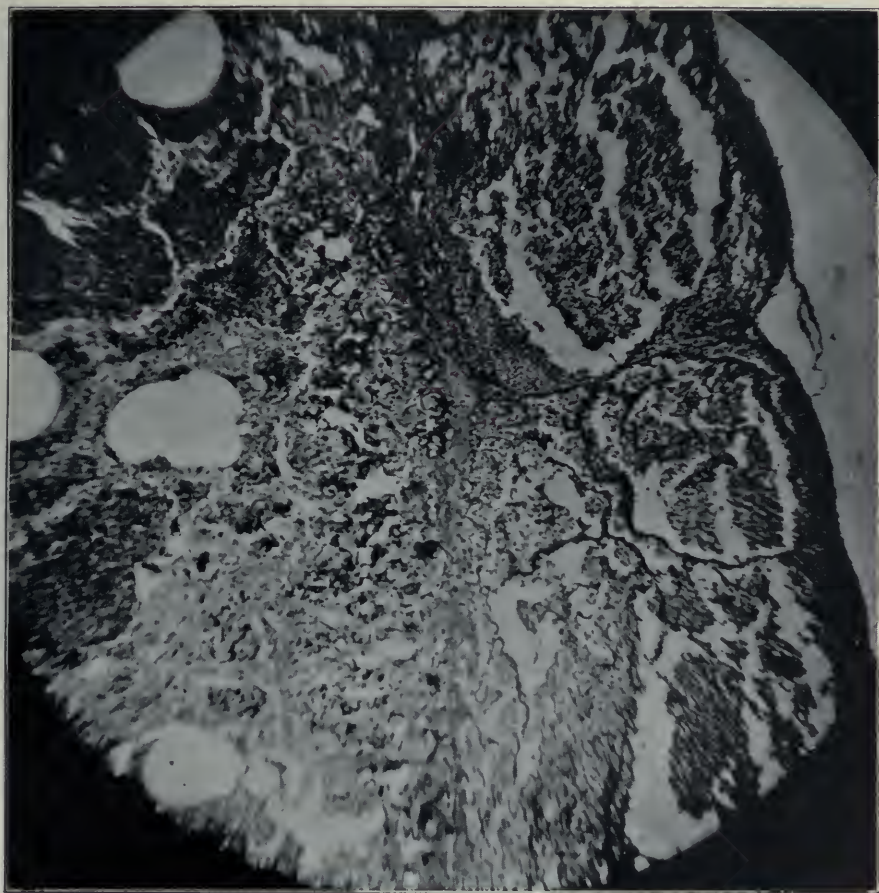


Fig. 3.—Section of lung showing a pleural lesion in a case of interstitial pneumonia caused by the hemolytic streptococcus.

red to a light grayish-red, or grayish-yellow, and varied in size from one or two centimeters in diameter up. It was very common to find areas of different color and consistency in the same lobe. In the lower lobes these areas were largest and most confluent, so that at times it was difficult to say whether or not the consolidation was homogeneous. In such cases, however, the upper lobes always showed distinct patchy consolidation.

The microscopic picture is shown in the accompanying illustrations. Its characteristic features were the intense edema and congestion of all interstitial tissues, the marked predominance of bloody exudate in the alveoli in most cases, and the irregular distribution of the lesion, not strictly peribronchial nor diffuse, but showing areas at different stages of development in the same section.

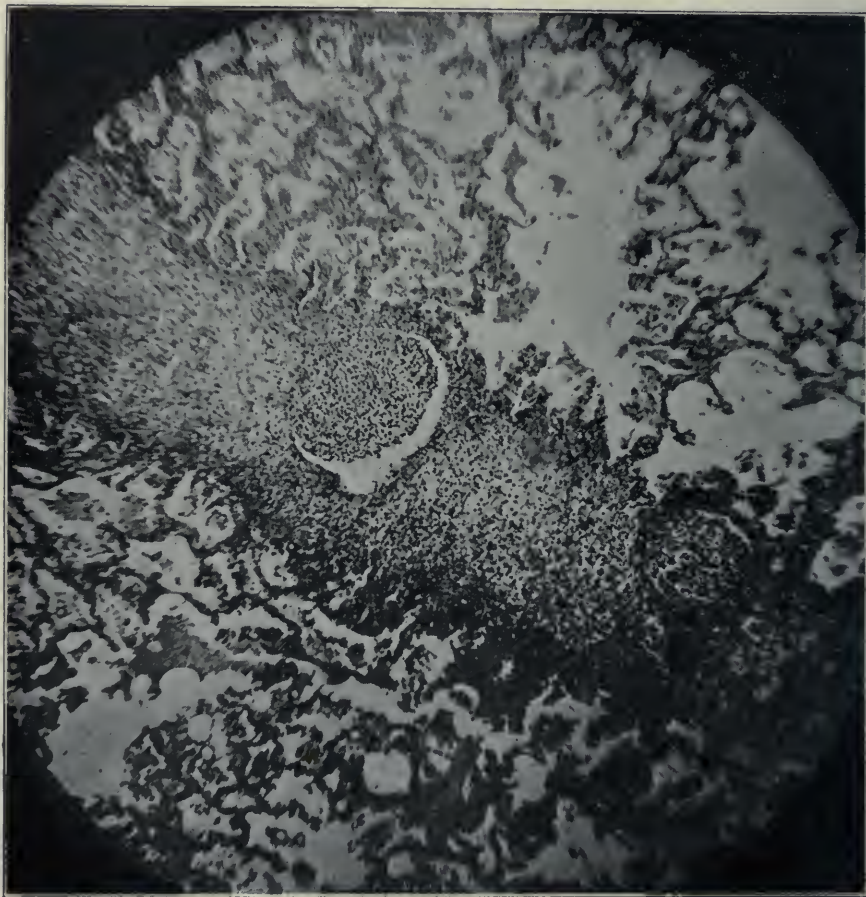


Fig. 4.—Section of lung from a case of interstitial pneumonia caused by the hemolytic streptococcus.

The question might here be raised whether it is not desirable to drop the term pneumonia as used to cover a pathologic condition so variable in its manifestations and etiology. Careful reading of reports from various hospitals leads to the firm belief that the clinical diagnosis in a large percentage of cases cannot be made to conform with the pathologic lesion — lobar pneumonia, bronchopneumonia and inter-

stitial pneumonia. Medical men, generally, have used the terms lobar and bronchopneumonia rather loosely, the diagnosis usually being based on the presence of consolidation of a part or the whole of one or more lobes.

In spite of the reports made by such workers as Cole and his associates at the Rockefeller Institute, knowledge of the bacteriology of pneumonia has been rather vague. With the unhappy experience with pneumonia, in both civil life and in the army, especially in the fall of 1918, large numbers of medical men have come in contact with the disease in a form exceeding in amount and variety of manifestations anything in their previous experience. If changes in the nomenclature can be made so as to indicate a difference in the prognosis, treatment and the complications to be looked for, much will be accomplished.

Another advantage would be attained in emphasizing the varieties of infecting organisms. The inclusion of pneumonia among the acute infectious diseases is comparatively recent. It is probable that the day of treating such cases in a general medical ward is past, and yet we have scarcely entered into the practice of isolating the various types of pneumonia. It is just as undesirable to expose a case of "acute lobar pneumonia," to an "acute streptococcus pneumonitis" as to expose any general medical case to either of the above. Isolation of the various types of pneumonia will probably be practiced generally in all well conducted hospitals. In such places with adequate laboratory facilities there will be no reason for doing otherwise.

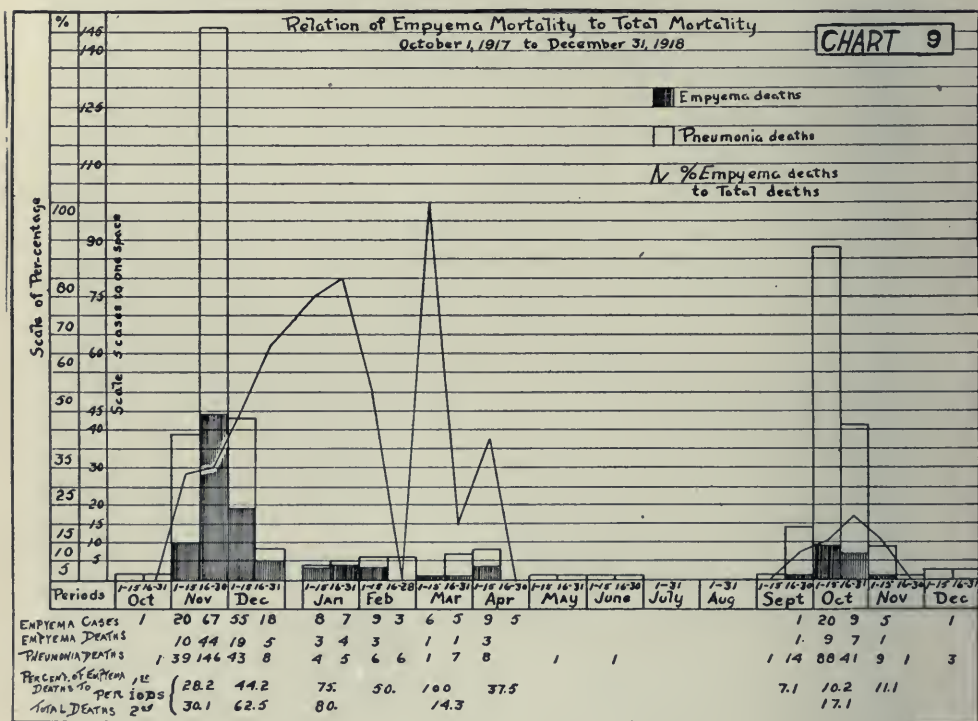
In private practice it is probable that the average physician must look to the state or municipal laboratory for sputum type differentiation, as he now does for examination for Klebs-Loeffler bacilli. Unquestionably, some health departments will provide specific serum, and provide for its administration. Such type differentiations, when incorporated as a part of the diagnosis, will serve to accentuate the importance of avoiding cross infections by using all the present methods of prophylaxis and stimulating their further development. Would it not, therefore, be well to do as has been done with "rheumatism"—reserve the diagnosis "acute lobar pneumonia" for those cases of epidemic pneumonia which are fairly well defined clinically, and due either to Type I pneumococcus, with its specific serum, or to the fixed types of pneumococci, I, II and III, and apply the term "acute pneumonitis," giving the causative organism whenever possible, to the various other conditions now called lobar, interstitial, lobular pneumonia or bronchopneumonia, septic or terminal pneumonia, etc.<sup>22</sup>

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2. Hamburger and Fox in reporting on pneumococcus and streptococcus infections at Camp Zachary Taylor used the term "pneumonitis."

## COMPLICATIONS

Empyema: Of the 2,344 cases of pneumonia, 249 developed empyema, an incidence of 10.6 per cent. This incidence was a steadily decreasing one for the three periods, being 16.5, 9.5 and 4.3 per cent., respectively. Period 1 furnished 41.5 per cent. of the total pneumonias, and 64.6 per cent. of the total cases of empyema, whereas Period 3 furnished 35.5 per cent. of the total pneumonias, and only 14.4 per cent. of the total empyemas.



## DIAGNOSIS

The diagnosis of pus in the chest is very difficult in certain cases, much less so in others. This depends largely on the character, amount and location of the effusion, and whether or not it occurs early or late in the course of the pneumonia. Its recognition often demands all the aids to diagnosis that can be summoned. The diagnosis rests on one or more of the following: (a) Change in condition of patient; (b) physical signs; (c) roentgenography and fluoroscopy; (d) sometimes, though not often, a change in the leukocyte count and increase in the number of polynuclear cells may be helpful.

(a) Change in Condition of Patient: During the course of the pneumonia there comes a time, usually between five and ten days, when in the absence of extension of the process the temperature, together with the pulse and respiratory rates, should fall, either by crisis or lysis. If this fails to occur, and especially if the remissions increase, suspicion should be aroused. In some cases the temperature falls to normal; after a varying number of days an afternoon rise of temperature begins. We have had cases in which pus was present where the temperature fell to normal after the primary pneumonia, and did not rise again above 99 F. until after the pus had been evacuated. Chills and sweating have been rare. Where the rise in temperature persists, or when convalescence is slow, pus must always be suspected. Many cases have ultimately been diagnosed where the first suspicion was raised by the very slow convalescence and the presence of pus or tuberculosis were considered most probable.

(b) Physical Signs: The physical signs have been notably irregular, and no wonder when one considers the multiplicity of conditions existing. The fluid may vary from a thin, dirty (dishwater) sero-fibrinous exudate, slightly greenish in color, as in the early hemolytic streptococcus fluids, to a dense creamy pus in some pneumococcic infections. In between are all gradations.

In our experience dulness, with a change in breath and voice sounds, sometimes a diminution, more frequently bronchophony or egophony, are the best indications for requesting a roentgen-ray examination, even though this may be limited to a fluoroscopy.

With supporting evidence from these aids, and sometimes without, no hesitation has been felt in inserting a needle one or many times. In many hundred cases needled, the only mishap has been the occasional entrance of air into the pleural cavity, which was of no serious import. A particular precaution we have practiced is that the needle, once inserted, is always withdrawn to the inner surface of the chest wall before changing the direction in order to explore a different area. This is done to avoid tearing the lung tissue. The point of insertion is over the area of maximum signs, since the rule rather than the exception is for the pus to be pocketed. In a few cases marked sensitiveness on percussion has helped to locate the pus.

Often signs are misleading, but a good rule is to insert the needle if there is a reasonable basis for believing pus to be present. Fluid has been obtained in areas over which there was dulness rather than flatness, with a friction rub and vocal fremitus present, and little change in voice or breath sounds. On the other hand, areas over which there was flatness, absence of vocal fremitus and markedly

diminished breath sounds, have frequently failed to show fluid. In the latter case the probability is that there was a dense fibrinous pleurisy, with little serous element. Sometimes, after a dry tap, a small drop of pus has appeared at the site of the puncture following the withdrawal of the needle.

(c) Roentgen-Ray Examination: The use of the roentgen ray has been of the greatest assistance in diagnosis.

The relation of the organism found in the pleural fluid to the predominant organism of the sputum is shown in Table 14. The mortality of 19 per cent. in pneumococcus infections, as compared with 33 per cent. in streptococcus and mixed infections, is in accord with the situation as reported from many other hospitals.

Table 15 gives the procedure in empyema for all periods. Of the 221 cases diagnosed previous to death, 150, or 67.9 per cent., occurred in Period 1. Of these 150 patients, 121 were operated on, with a mortality of 34 per cent. Of the twenty-nine patients not operated on, twenty-six died, a mortality of 89 per cent. Twenty-one of the twenty-nine died after the diagnostic puncture. These men were practically moribund at the time of diagnosis, too sick to withstand the shock of operation. The operation of choice has varied with the several chiefs of the surgical section. In Period 1 it was costatectomy, thoracotomy being done in the bad risks. Of the fifteen patients on whom a thoracotomy was done, eleven died, a mortality of 73 per cent.

Choice of the Time of Operation: As in most hospitals, the early practice was to operate as soon as the diagnosis was established. The result was a very high immediate operative mortality. In the streptococcus infections, especially where a purulent pleuritis developed early, prompt operation usually meant a collapsed lung on the operated side, and very possibly the opposite lung was consolidated, with little functioning lung tissue remaining. These operations, performed at the height of the toxemia, meant death, either from shock or asphyxiation. With this experience in view, aspiration was done every second day for a certain period and the intervals gradually increased thereafter.

The transition from the thin fluids commonly present in the streptococcus infections to a thick pus, occurs in a variable time. Frequently this has occurred in forty-eight hours. Ten to twelve days is the most frequent interval. Generally speaking, the longer away it is possible to get from the acute infection, the more favorable the end result. If, by repeated aspirations, the general condition improves, these should be continued. In the average case the pus will ultimately become so thick as to render further aspiration impossible. In a certain number of cases, even though aspiration is still possible, the general condition of the patient becomes worse, the pulse rate increases, the temperature

becomes irregular, with an increasing height in the evening. Chills and sweating are rare in these cases.

In many cases, even with the general condition of the patient fairly satisfactory, the time will come when operation, with irrigation, promises a more rapid recovery than continuous aspiration. In Period 1 many patients were admitted with thick pus already formed, too thick to be withdrawn through a large needle. These patients were too sick to justify being sent to the roentgen-ray department for a picture.

*Medical Care.*—Postoperative care, aside from careful attention to drainage and irrigation, is largely a medical one. Attention to nutrition, the question of cardiac stimulation, frequent and careful examinations of the chest for signs of accumulation of pus, pericardial effusions, etc., are the most important points. Later it is a matter of "conditioning," breathing and carefully graduated setting up exercises, hikes, games, etc.

In our opinion, this attention can best be given by retaining these patients on the Medical Section with one or more qualified surgeons assigned to this section for the necessary operative work, irrigations and dressings. It is essential that a man filled with enthusiasm for his work, and possessed of the necessary surgical technic, should receive such an assignment.

*Metastatic Abscesses.*—Metastatic abscess, single or multiple, occurred in seventeen cases of pneumonia. Of these seventeen cases four accompanied empyema. Five came to necropsy, three not being diagnosed before death. One of these undiagnosed cases was a small abscess in the first intercostal muscle; a second case was a perirenal abscess. The most interesting cases of this group were five cases in which a painless tumor was noted just above the symphysis pubis, not red and not tender to pressure. The first of these cases (Reg. No. 2422), was not recognized until there appeared a rounded tumefaction exactly in the midline, extending about two inches above the symphysis pubis. The tumor was thought to be a distended bladder, but on catheterization a very small amount of urine was obtained. One hundred cubic centimeters of salt solution was introduced into the bladder, and the same amount was withdrawn. The tumor was still present. The possibility of a diverticulum of the bladder was considered. There was no increase in temperature, and no muscular rigidity. During the next six days there was a slight, but constant, increase in the size of the tumor, the patient meanwhile voiding a normal amount of urine. On the sixth day fluctuation was obtained. An incision was made and about 150 c.c. of thick pus was found between the right rectus muscle and

its posterior sheath. Culture showed a pneumococcus—type undetermined. The other cases presented practically the same picture, except that in three the tumor was slightly asymmetrical.

*Subcutaneous Emphysema.*—Generalized subcutaneous emphysema, as a complication of pneumonia, occurred in eight cases, seven white men and one colored man. Three of these patients recovered.

The onset of the emphysema appeared to be definitely associated with an unusually severe paroxysm of coughing in one case. Hoarseness and increased dyspnea were the only symptoms apparently referable to this complication.

The tissues of the neck, posteriorly especially, but also in the supraclavicular region, were involved in all the eight cases; the interscapular region was involved in four; the axillae and pectoral region in three; the face in three; the flanks and thighs in one.

The three patients who recovered had a prolonged convalescence. Each one had a persistent hoarseness. Laryngeal examination showed only an acute laryngitis, which disappeared slowly. One patient has since been found to have pulmonary tuberculosis.

Anaerobic antemortem blood cultures were sterile in two cases; in the third case they showed pneumococcus—type undetermined.

Of the postmortem cases all showed emphysema of the mediastinal connective tissue, in addition to the evident subcutaneous emphysema noted during life. Petechial subpleural hemorrhages were evident in two cases. Free air beneath the visceral pleura, especially along the interlobular spaces and lung fissures, was seen in two cases. One case showed confluent patches of consolidation having undergone softening and produced abscess cavities. Microscopically, small areas of hemorrhage were frequent in these cases as in other pneumonia cases of the same period.

In addition there were ten cases of emphysema of mediastinal tissue diagnosed only at necropsy.

Bacteriologic study of the mediastinal tissue showing marked emphysema was attempted in eight cases with the following results on culture:

No growth .....	3
Pneumococcus Group IV .....	3
Streptococcus, nonhemolytic .....	1
Streptococcus, hemolytic .....	1

In each case the organism present was also found in the blood stream.

In one case with most marked subcutaneous emphysema before death, an emulsion of emphysematous tissue was injected intravenously

into a rabbit. The rabbit was killed in five minutes and placed in the incubator for eighteen hours. All organs, as well as heart's blood, gave a pneumococcus Group IV which was also isolated from the heart's blood of the patient.

#### SUMMARY

A large percentage of the cases of pneumonia here presented followed an epidemic of measles and an epidemic of influenza. Following the epidemic of measles, the predominance of hemolytic streptococcus as the infecting organism determined the high mortality and the high incidence of complications; especially empyema.

Following the epidemic of influenza the incidence of hemolytic streptococcus was less, but when present the lesions produced did not vary from those present in cases of the year previous. In addition to the streptococcus infections there was a large group of cases of mixed bacteriology with pneumococcus, especially Group IV, predominating.

During the greater part of the period, January to September, 1918, the character of the infection, mortality and complications were not essentially different from those occurring ordinarily. Throughout the first part of this period, pneumococci of fixed Types I and II were found in approximately the same proportion of cases as when these types were first described. From that time on they declined steadily until less than five per cent. of the cases showed their presence.

Definite evidence of the presence of the *B. influenzae* as a determining factor in pneumonias following the epidemic of the fall of 1918 was not obtained at this hospital. The epidemic, whatever its etiology, caused a lowering of resistance which favored invasion by organisms identical with those which observation during nonepidemic periods had shown to be present in the upper respiratory tract of individuals not suffering from pneumonia.

Postmortem studies show that the pneumococcus is constantly present in lobar pneumonia, while the hemolytic streptococcus, with a variety of other organisms, and the pneumococcus, is found in bronchopneumonia.

Comparison of sputum examinations with more accurate bacteriologic data from the same cases, has shown correspondence in a large percentage. If the sputum examination is made with a view to determining the predominating organism present, its value is greatly enhanced and in this form it is one of the valuable diagnostic procedures in pneumonia.

Clinical differentiation between lobar and bronchopneumonia to accord with postmortem findings has been impossible. For this reason it is suggested that the term acute pneumonitis, followed by a statement of the predominating organism in the sputum, be used to desig-

nate those cases of pneumonia which are not frankly lobar in type, but caused by one of the fixed types of pneumococcus.

The incidence of empyema was highest among the pneumonias following measles. For the entire period, cases complicated with empyema constituted 10.6 per cent. of the total pneumonias, and furnished 25.6 per cent. of the total pneumonia deaths.

The appearance of the pleural exudate caused by the *Streptococcus hemolyticus* was characteristic. Repeated aspiration of such fluids, followed by operation after the acute pneumonitis has subsided, has given the more satisfactory results at this hospital.

The occurrence of encapsulated pus was very common, especially in the streptococcus infections. These pockets were frequently multiple and offered great difficulties from an operative standpoint.

## CRITERIONS FOR DISTINGUISHING THE ENDAMOEBIA OF AMEBIASIS FROM OTHER ORGANISMS \*

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The practitioner and clinical microscopist undertaking to make a critical diagnosis of the pathogenic ameba, *Endamoeba dysenteriae*, in either acute, chronic or latent amebiasis, is beset by certain practical and technical difficulties, which, under certain conditions, may become perplexing or even baffling, unless he has had some experience in dealing with the various forms of this ameba and its associated organisms of the human digestive tract. These difficulties have been cleared up somewhat, although the complexities of the situation have been increased somewhat, by the distinction of another very common, tetragenous ameba in human feces in addition to *E. dysenteriae*, by Wenyon and O'Conner,<sup>1</sup> namely, *Endamoeba nana*, a seemingly non-pathogenic species whose dimensions, number of nuclei, and clear pseudopodia do not differentiate it from the pathogenic form with which it may be associated. We have elsewhere shown<sup>2</sup> that this new endameba is the commonest intestinal ameba in American troops, in which we found 325 cases among 1,200 overseas troops, and ninety-two cases in 300 home service troops, a total of 417 in 1,500 men, or 28 per cent., while there were only 389, or 23 per cent., infections with *E. coli*, and 139, or 9.3 per cent., with *E. dysenteriae*. Of the latter, 130, or 10.8 per cent., occurred among the 1,200 overseas men.

From recent European findings and our own results it appears that *E. nana* in man has a very wide geographic distribution. In actual numbers its cysts far exceed those of the cysts of *E. coli* and *E. dysenteriae* in our experience. It is, therefore, to be expected that this endameba will appear rather frequently in stools examined in this

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\* From the U. S. Army Laboratory, Port of Embarkation, New York City; Major E. H. Schorer, M. C., U. S. Army, officer-in-charge.

1. Wenyon, C. M., and O'Conner, F. W.: Spread and Incidence of Protozoal Infection in British Troops, J. Roy. Army Med. Corps, Lond. **28**:1, 1917.

2. Kofoid, C. A., Kornhauser, S. I., and Plate, J. F.: On Intestinal Parasites in Overseas and Home Service Troops of the U. S. Army, with Special Reference to Carriers of Amebiasis, J. A. M. A. **72**: 1919.

country, and the examiner must be prepared to distinguish *E. dysenteriae* not only from the well known *E. coli*, but also from this *E. nana*. The criterions employed in the former case are not applicable in the latter.

Moreover, there are several organisms whose cysts may have about the same size, from 7 to 10 microns in diameter, and are sometimes of the same spheroidal shape, at least in some of the individuals, and unstained or in iodine-eosin have much the same optical properties and colors, as the smaller races of *E. dysenteriae*. These organisms are the occasionally spheroidal cysts (Fig. 15) of *E. nana* (usually ellipsoidal), and those of the flagellate *Chilomastix mesnili* (Fig. 32) (usually pyriform), the larger and more rotund individuals of a large race or species (Fig. 35) of the common intestinal yeast (usually ellipsoidal), the central, homogeneous body of *Blastocystis hominis* (Fig. 33) in unstained material, and certain spheroidal spores of a mold (Fig. 43) occurring in stale stools. The ovoidal cysts of an unknown organism (Fig. 34), certain homogeneous spheres (Fig. 39), and leukocytes in various phases of degeneration, add to the complex of organisms or parts thereof, from which the cysts of the organism of amebiasis must be distinguished critically. Not infrequently *E. dysenteriae* occurs coincidentally with one or both of the other two species. It was found with both in forty-one cases of the 130 infections found in 1,200 overseas troops, with *E. nana* only in forty-four cases, and with *E. coli* alone in fifteen cases. It was found without other endamebae in only thirty of the 130 cases of infection. Mixed infections with *E. dysenteriae* appear to be the rule rather than the exception.

#### FREE STAGES

In cases of acute amebic dysentery the large, free *E. dysenteriae* are readily distinguished from *E. coli* by their ingested red blood corpuscles, their clear, hyaline pseudopodia, and their very active locomotion. *E. coli* rarely ingests corpuscles, has granular pseudopodia, and is sluggish in movement. The smaller races of *E. dysenteriae* in the free state are to be distinguished from *E. nana* of comparable size in the free state with difficulty and mainly by the structure of the nucleus, preferably in stained preparations.

In a case of infection by *E. nana* alone which was under daily observation we have found that the free phase of the species appears rarely in the usual formed stools, but may occur in large numbers in liquid stools after a saline purge. In the sluggish free stage of formed stools the pseudopodia (Fig. 15) are single, broad, terminal on the elongated body, and hyaline. In the more liquid stools the amebas on the warm stage are very active and send out smaller, more slender,

hyaline pseudopodia in various directions. These pseudopodia seem to be more numerous and smaller than in *E. dysenteriae* of comparable size but are not always so and do not afford a critical criterion for distinguishing them from *E. dysenteriae*, owing to their variability with the physiologic state of the individual ameba. The presence of highly refractive, bacteria-filled food vacuoles in *E. nana* is sometimes of value as indicating the probability that the ameba in question is that species, but these vacuoles are quite variable in appearance and occurrence and are therefore somewhat unreliable as a criterion.

There is always available, however, an absolutely diagnostic criterion for the separation of the free stages of *E. dysenteriae* from those of *E. nana*, namely, the structure of the nucleus as it appears in the stained slide. In *E. dysenteriae* (Figs. 1-11) there is a central karyosome and the peripheral chromatin is scattered over the nuclear membrane somewhat uniformly in plaques or granules of small size. In *E. nana* (Figs. 12-23) there is no central granule and the peripheral chromatin is massed in a single large clump at one point on the nuclear membrane. These nuclear contrasts may sometimes be made out in the living material or in iodine-eosin, but are perfectly distinct in amebas stained in iron hematoxylin.

#### ENCYSTED STAGES

In cases of chronic and latent intestinal amebiasis, and in carriers, the evidence of infection will be determined mainly by the encysted stages which occur in formed stools, or in the semifluid ones which often characterize such cases. Free amebas are usually rare or absent in such stools. The determination of infection in such cases rests wholly on the microscopic analysis of the encysted stages of these intestinal amebas and associated organisms of the digestive tract.

*Methods.*—The most useful method for this analysis, in our experience, has been the direct smear with Donaldson's<sup>3</sup> iodine-eosin stain. The original formula for this is as follows: Five per cent. aqueous solution of potassium iodide saturated with iodine, one part; saturated aqueous solution of either eosin or Rubin S, one part. Mixed fresh each morning.

By a curious error reviews of this paper in the *Tropical Disease Bulletin* and the *Bulletin of the Institute Pasteur* add ether to this formula. We have found in practice that the volumes of the component solutions may be modified to advantage, owing, perhaps, to varying efficiency of the eosin. We have made these solutions in physiologic salt solution and reduced the proportion of iodine as fol-

3. Donaldson, R.: Method of Detecting Protozoal Cysts in Feces by Means of Wet Stained Preparations, *Lancet* 2:571, 1917.

lows: Saturated solution eosin in normal salt solution, two parts; 5 per cent. potassium iodid in normal salt solution saturated with iodine, one part; normal salt solution, two parts.

The smear is prepared for microscopic examination by rubbing out a minute bit of the feces by rolling it on a round applicator stick in a small drop of normal salt solution and then in an adjacent drop of iodine-eosin stain. A single cover is placed on both drops and the smear is ready for immediate examination. Living flagellates and unstained cysts appear in the unstained part. In the stained area the bacteria, fecal particles and the intestinal yeasts (except the larger forms) stain at once. Against the pink background the protozoan cysts stand out clearly as bright spherules which soon become tinged with the iodine to varying tones of yellow, while their glycogen filled vacuoles, when present, turn light or dark brown according to their mass. The nuclei become more clearly defined as the iodine penetrates, especially in *E. coli* and *E. dysenteriae*. They are detected with difficulty in this stain in *E. nana*.

We have used the concentration method of Cropper and Rowe<sup>4</sup> as modified by Boeck<sup>5</sup> on over 1,500 stools, as supplemental to the direct smear, but have added less than 10 per cent. to the infections detected by the direct smears. A few trials of the Carles-Barthelmy<sup>6</sup> citric formalin method have also been made. These added infections have been mainly of *E. coli*, which is rarely abundant, a few light infections of *E. nana* and a few cases of *Giardia*. It is probable that the detection of light infections of *E. dysenteriae* would be facilitated by these methods, but the time required is greater and the percentage of infection of pathogenic organisms detected thereby very small. The direct smear is simple, rapid and in our experience both efficient and reliable for practical purposes. Concentration methods are useful in research and in following up difficult and suspected cases.

#### CRITERIONS FOR DISTINGUISHING INTESTINAL ENTAMEBAS

The following tabular view of the distinctions will facilitate quick comparison of the diagnostic features of the species of entameba. The analyses made by Dobell and Jepps,<sup>7</sup> Mathews<sup>8</sup> and Smith<sup>9</sup> have

4. Cropper, J. W., and Rowe, R. W. H.: A Method of Concentrating Entameba Cysts in Stools, *Lancet* **2**:63, 1917.

5. Boeck, W. C.: Rapid Method for Detection of Protozoan Cysts in Mammalian Feces, *Univ. Calif. Pub. Zool.* **18**:145, 1917.

6. Carles, J., and Barthelmy, E.: Procédé special pour collecter les kystes dysenteriques contenus dans les selles, *C. R. Soc. Biol., Paris*, **80**:402, 1917.

7. Dobell, C., and Jepps, M. W.: On the Common Intestinal Entamebas of Man, and Their Differential Diagnosis, *Brit. M. J.* **1**:607, 1917.

8. Mathews, J. K.: Observations on the Cysts of the Common Intestinal Protozoa of Man, *Ann. Trop. M. & Parasitol.* **12**:17, 1918.

9. Smith, A. M.: Measurements and Observations on the Cysts of *Entameba histolytica* and *Entameba coli*, *Ann. Trop. M. & Parasitol.* **12**:27, 1918.

been helpful in its preparation. In this table the criterions are stated succinctly without the essential qualifications which will be discussed later.

TABLE 1.—DIAGNOSTIC FEATURES OF ENDAMOEBIA DYSENTERIAE, *E. NANA* AND *E. COLI*

Criterion	<i>E. dysenteriae</i>	<i>E. nana</i>	<i>E. coli</i>
Size	(5) 6-15 (20) microns	(3) 5-12 (16) microns	(11) 14-22 (35) microns
Shape	Spheroidal, sometimes asymmetrically rounded	Ellipsoidal in smaller forms, ovoidal in larger; frequently irregular, sometimes spherical	Spheroidal, sometimes ellipsoidal, ovoidal or irregular
Optical properties, unstained	Most highly refractive, glassy, often irregularly vacuolated; light grayish blue; nuclei rarely visible; glycogen mass not visible.	Less highly refractive but with highly refractive granules, grayish blue; nuclei invisible; glycogen mass distinct	Least highly refractive, homogeneous, porcellaneous, grayish blue; nuclei faintly visible; glycogen mass faintly visible
Stained with iodine-eosin	Cytoplasm bright greenish yellow; coarsely vacuolated, in small races evenly but finely granular Nuclei distinct with highly refractive, thick border and distinct central granule Glycogen diffuse; if massed, with vague limits Cyst stains red more quickly	Cytoplasm greenish yellow with numerous small refractive vacuoles Nuclei indistinct, with thin border and peripheral chromatin blob Glycogen dense, in one or more large sharply defined masses, seldom central Cyst resists stain longer	Cytoplasm coarsely uniformly granular; yellowish brown Nuclei very distinct with thin granular borders and central granule Glycogen central with vague borders Cyst usually resists stain longer
Nuclei: number	1—30-45% 2—13-30% 3—rare 4—25-55%	1—Very common 2—Less common 4—Common in small race, very rare in large one	1—Very rare 2—Rare 4—Very rare 8—Very common 16—Very rare
Structure	Central granule distinct; peripheral chromatin distributed rather evenly in small plaques	No central granule; nuclear membrane indistinct; peripheral chromatin gathered in a single blob on the membrane	Central granule distinct, peripheral chromatin in a few large plaques on the nuclear membrane
Chromatoid substance	In one stout bar or several slender bars with rounded ends. Present in about 50% of the cysts	In several rounded or irregular masses. Rarely present	In stout or slender splinters with square or sharp ends. Present in about 5-10% of the cysts
Cyst wall	Thin, distinct	Variable, less distinct	Thicker, very distinct
Size races	Very evident. Small race at 7 microns, large race at 13-14 microns, and one at 10 microns are the most frequent	Very evident. One at 5-7 microns, and one at 8-10 microns, and probably a still larger one at 12-15 microns, most frequent	Less evident. Probably one at 15, one at 18 microns and one larger

The table shows far less fully than the material itself the great variability in the criterions which are available to distinguish these three species. It should be borne in mind, however, that every case of infection will generally afford some individual amebas on which

a diagnosis may be made clearly and unequivocally, although there may be some individuals that are indeterminate and others of questionable allocation. Abnormal, moribund and pathologic states are to be expected in these parasitic species.

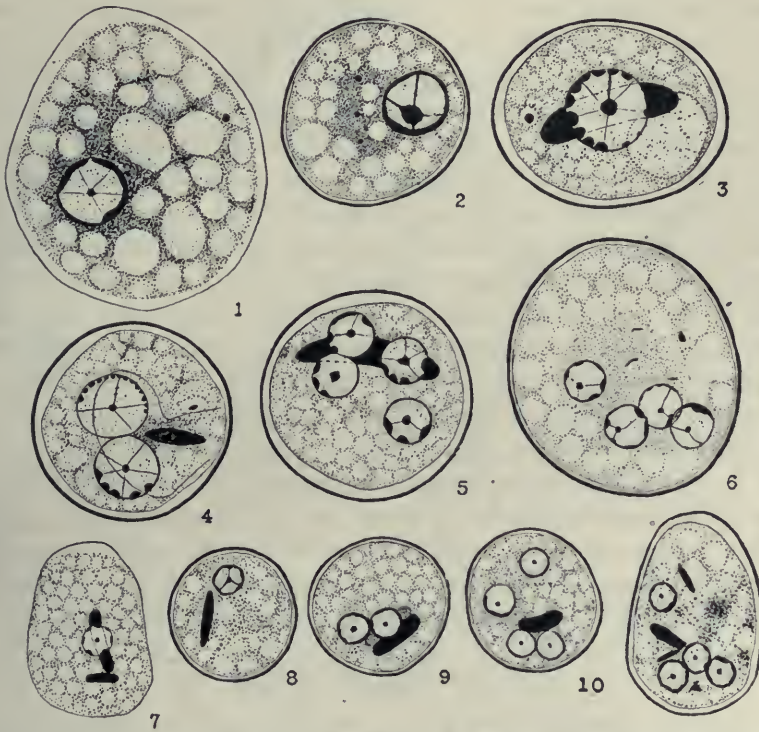
Infections of *E. coli* are usually readily distinguished at once in iodine-eosin by size, color and granulations of the cytoplasm, as well as by the prevalent eight nucleate cysts. Individuals are relatively rare in most infections by this ameba.

Infections by *E. nana* are distinguished by the abundance of cysts, the large, clearly defined glycogen mass when present, the prevalence of ellipsoidal or ovoidal cysts, the abundance of highly refractive granules, and, preferably in stained material, the absence of central granule and the clumping of the chromatin on the nuclear membrane in a single blob.

In infections by *E. dysenteriae* the cysts are generally less abundant than in those by *E. nana*, and are distinguished by their glassy, refractive, irregularly vacuolated or (in small cysts) almost homogeneous cytoplasm, with distinct nuclei with central granule and heavy rim, never exceeding four in number, with relatively abundant mononucleates and glycogen, when present, diffusely distributed.

#### ENDAMOEBIA DYSENTERIAE

Cysts are usually spherical and fall into three general groups according to size, the largest being from 12 to 14 microns in diameter and the smallest from 7 to 8 microns. A medium sized race of from 10 to 11 microns is less abundant. However, individuals ranging from 5 to 20 microns may be found. The cyst wall is thin and rather easily penetrated by the iodine-eosin stain and by hematoxylin stains. In the iodine-eosin stain the cytoplasm is first a bluish gray which changes to a yellow and then to a pink color, which gradually deepens to red. The cytoplasm is unevenly vacuolated and is very finely granular but the granules are not so evenly distributed as in *E. coli*. The glycogen mass, when present, stains a light brown in iodine-eosin, the edges gradually shading into the surrounding cytoplasm. Sometimes its glycogen is diffused throughout the entire cyst which then stains a yellowish brown color. Chromatoid rods are found in a majority of the cysts, represented by either one large rod with blunt ends nearly the diameter of the cyst in length, or by several smaller rods scattered irregularly in the cytoplasm. These rods are seen in a 0.01 per cent. solution of Janus green in physiologic salt solution after a few minutes application as definite, bluish, highly refractive bodies with clear cut outline. They also stain deep black in Heidenhain's iron hematoxylin.



Figs. 1 to 6.\*—Large races of *Endamoeba dysenteriae* (10-17 microns) stained with iron hematoxylin,  $\times 2800$ . (1) Relatively small, free amoeba in contracted condition, showing clear, peripheral ectoplasm; 17 microns. (2) Mononucleate cyst with peripheral chromatin uncontracted and no chromatoidal body; 10 microns. (3) Same, with large, stout chromatoidal rod; chromatin on nuclear membrane gathered in small clumps; large glycogen vacuole in cytoplasm; 10 by 13 microns; (4) Binucleate cyst with small, fusiform chromatoidal rod and slender, coiled thread; 11 microns. (5) Quadrinucleate or tetragenous cyst with large chromatoidal rod; 12 microns. (6) Largest race of *E. dysenteriae* four nuclei; no chromatoidal rod; 14 microns.

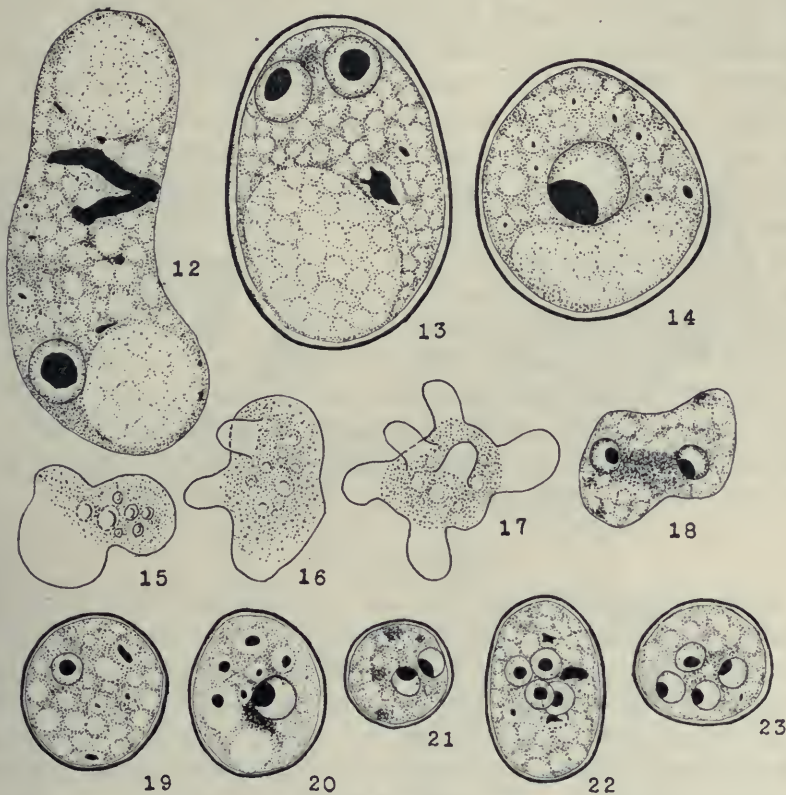
Figs. 7 to 11.—Small races of *Endamoeba dysenteriae* (7-10 microns) stained with iron hematoxylin,  $\times 2800$ . (7) Small, free amoeba evidently approaching encystment; two chromatoidal bodies; 7 by 10 microns. (8) Small mononucleate cyst with slender chromatoidal bar; 7 microns. (9) Small binucleate cyst with two chromatoidal bars; 8 microns. (10) Small quadrinucleate cyst with stout chromatoidal body; 8 microns. (11) Ovoidal cyst with four nuclei and three chromatoidal bars; 7 by 11 microns.

\*All drawings have been made by Dr. Olive Swezy under a grant from the Division of Medicine and Related Sciences, National Council of Research.

The nuclei are one to four in number. They should appear distinct and well defined in cysts penetrated by iodine-eosin stain. The chromatin appears to be evenly distributed on the nuclear membrane which seems to be thicker than in *E. coli*, and there is present a distinct central granule. At sharp focus each nucleus should be seen as an even circle of highly refractive material, with a clearly defined central dot. A critical examination of the nuclei is absolutely essential in making the determination. It is advisable to roll the cyst by a slight pressure on the cover glass, so that the nuclei may be studied from various angles, counted and proved to be characteristic for *E. dysenteriae*. Cysts of small races are at times difficult to determine and permanent hematoxylin preparations may be necessary to arrive at a definite conclusion. In iron hematoxylin preparations the nuclei stain very definitely after fixation in modified Schaudinn's fluid. The peripheral chromatin does not appear so evenly distributed on the nuclear membrane as in cysts stained by iodine-eosin, being found as many more or less irregularly rounded plaques having small spaces between. This may be due in part to the method of fixation. The central granule is very definite and from it fibrils radiate to the chromatin plaques on the nuclear membrane. The fibrils often show a single granulelike thickening some distance from their central attachment. Unlike *E. coli* the nuclear material of this species takes a deep black stain readily.

#### ENDAMOEBIA NANA

Cysts are generally ovoidal or ellipsoidal but are occasionally spheroidal. The larger races are from 10 to 15 microns in diameter and usually ovoidal, the smaller races are from 4 to 8 microns and ellipsoidal. The cyst wall is thin, but distinct and is not easily penetrated by iodine-eosin stain, the cytoplasm remaining for a time grayish green. Glycogen is most abundant in large mononucleates and when present stains deep brown, showing that the iodine of the stain has penetrated but the eosin is excluded for many minutes. Dead cysts, however, stain deep red very quickly. *Endamoeba nana* stains well with iron hematoxylin. The cytoplasm contains many small vacuoles enclosing bacteria. These vacuoles are highly refractive and obscure the nuclei. The glycogen mass, which is frequently present, has a very definite outline, not shading into the surrounding cytoplasm, and is lateral in position. This mass dissolves out in the iron hematoxylin preparations, leaving a clear vacuole. The chromatoid body is made up of a mass of small rods irregularly clumped together, or in an amorphous mass. These may be seen in the hematoxylin preparations and some individuals are crowded with small chromatoidal granules.



Figs. 12 to 14.—Large race of *Endamoeba nana*, stained with iron hematoxylin,  $\times 2800$ . (12) Sluggish, free amoeba from formed stool, mononucleate with two empty glycogen vacuoles, a large, irregular chromatoidal rod, and several bacteria-filled food vacuoles. Chromatin clump of nucleus in face view; 9 by 22 microns. (13) Large, mononucleate cyst with glycogen vacuole, numerous food vacuoles, and chromatin clump in side view; 12 by 13 microns. (14) Binucleate cyst with large glycogen vacuole, large food vacuole, and chromatin clump in face view; 11 by 17 microns.

Figs. 15 to 23.—Small race of *Endamoeba nana* (6-8 microns), stained with iron hematoxylin, except figures 15 to 17, which were drawn from living specimens;  $\times 2800$  (15, 16, 17). Three successive positions of a small *E. nana*, from stool after saline purge, on warm stage; 8 to 10 microns. (18) Sluggish, binucleate, free amoeba with oblique and lateral views of peripheral chromatin clump; 5 by 9 microns. (19) Mononucleate cyst with several food vacuoles and no glycogen vacuole of chromatoidal body; 7 microns. (20) The same with small glycogen vacuole, numerous food vacuoles and no chromatoidal rod; 7 by 8.5 microns. (21) Minute binucleate cyst; 5.5 microns. (22) Ellipsoidal cyst with four nuclei; chromatin clumps in face view, three food vacuoles and an irregular chromatoidal body, 7 by 9 microns. (23) Quadrinucleate cyst with chromatin clumps in side or oblique view; 7 microns.

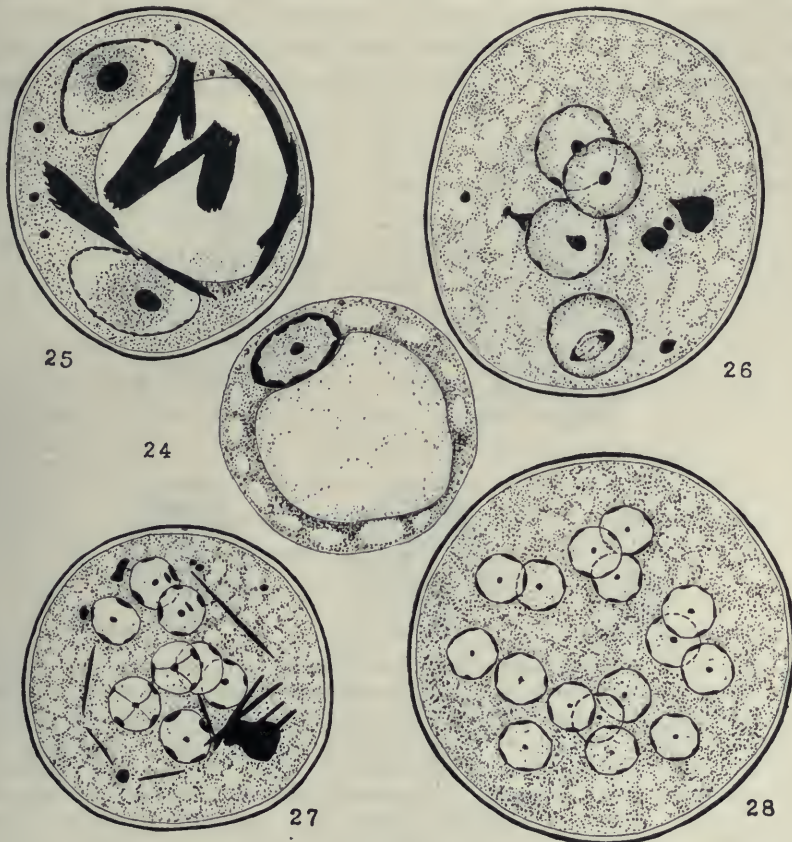
The nuclei are one to four in number and their structure forms the most important means of distinguishing the species. The characters are the absence of a central chromatin granule and the massing of the chromatin material in one or two large clumps or blobs on the nuclear membrane. The nuclei are not so easily seen in iodine-eosin stain as are those of *E. coli* and *E. dysenteriae*, but may often be found by careful searching with the oil immersion and rolling the cyst under the cover glass. In large *E. nana* cysts having a glycogen mass present there is generally only a single nucleus. Cysts of the small races seldom have glycogen present and they show four nuclei with massed chromatin. *E. nana* cysts well stained in iron hematoxylin show distinctly the massed chromatin in the nuclei and the absence of the central granules. In some instances a minute central or lateral granule connected by a fiber with the lateral blob of chromatin may be detected. In all doubtful cases such preparations examined with the oil immersion lens make a clear and unequivocal distinction between infections by *E. dysenteriae* and by *E. nana* possible and a definite diagnosis feasible.

#### ENDAMOEBIA COLI

Cysts are generally spherical and usually range from 14 to 22 microns in diameter. Elongated ellipsoidal cysts are often seen. The cyst wall is rather thick and clearly defined. It is rather easily penetrated by iodine-eosin stain but acts very erratically in regard to iron hematoxylin, either failing to allow the stain to penetrate, or holding it with great tenacity after staining and destaining more readily in some instances. In iodine-eosin stain the cyst first appears greenish yellow and may be picked up with the low power, standing out clearly against the pink background. Gradually, the color changes to a yellowish green and then to a light brown, but it is less readily tinged by the eosin of the stain than is *E. dysenteriae*. The cytoplasm is more coarsely but more uniformly granular than that of *E. dysenteriae*. The vacuolization in the eight-nucleate cysts is very uniform. Glycogen is rarely present except in cysts having fewer than eight nuclei. In binucleate cysts the glycogen appears in iodine-eosin stain as a large, squarish, rather definitely defined dark brown mass, filling the greater part of the cyst and crowding the two large, elongated nuclei peripherally in the cyst. The chromatoid bodies are rarely seen. In Janus green and in iron hematoxylin they appear, when present, as several sharp, pointed splinters lying in various directions in the cytoplasm of the cyst.

The nuclei are generally eight in number, but exceptionally large cysts may contain sixteen. They appear clear and definite in iodine-eosin stain and may be counted and studied without great difficulty.

Each nucleus has a central granule and peripheral chromatin situated in the nuclear membrane in uneven masses, giving, at sharp focus, a rather ragged inner edge to the refractive ring of chromatin material. In *E. dysenteriae* this inner edge is more even. In hematoxylin the nuclei are generally not so distinct as those of *E. dysenteriae* treated by

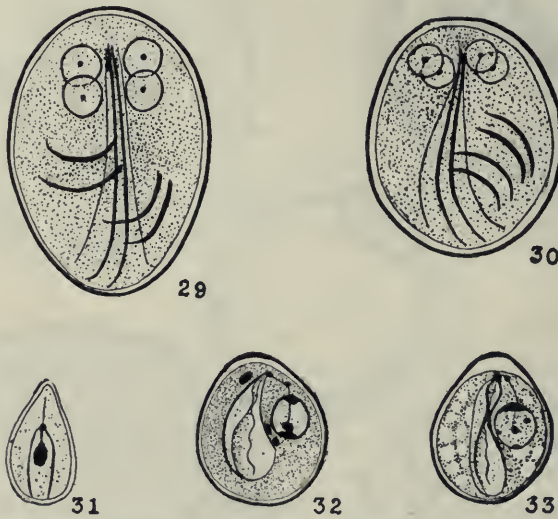


Figs. 24 to 28.—*Endamoeba coli*, stained with iron hematoxylin,  $\times 2800$ . (24) Mononucleate cyst with large glycogen vacuole; 12.5 microns. (25) Binucleate cyst; 15 by 17 microns. (26) Quadrinucleate cyst with irregular, deeply stained masses in the cytoplasm. Nuclei apparently in mitosis; 18 by 20 microns. (27) Cyst with eight nuclei, chromatoidal splinters, and deeply stained masses; 15 microns. (28) Cyst with sixteen nuclei. No chromatoidal splinters; 19 microns.

the same method, as the cyst either decolorizes too much or retains the stain throughout. For this reason the picture given by iodine-eosin is more distinct and therefore more satisfactory than that given by iron hematoxylin, especially in slides decolorized for *E. dysenteriae*.

## INTESTINAL FLAGELLATES: CHILOMASTIX MESNILI

The cysts of this flagellate (Figs. 29 and 30) are typically pyriform but are sometimes spherical, in which case they resemble superficially mononucleate *E. dysenteriae*. They often have diffuse or feebly massed glycogen, and sometimes show scattered, ellipsoidal chromatoidal inclusions in iron hematoxylin stain. The nucleus has a subcentral granule and massed peripheral chromatin. The most characteristic feature is the cytostomal or oral loop, which forms a characteristic dark, flattened ring visible in iodine-eosin stain in favorably oriented cysts. There



Figs. 29 to 33.—Flagellate cysts stained with iron hematoxylin,  $\times 2800$ . (29) Large cyst of *Giardia intestinalis* with two zooids; four anterior nuclei, two axostyles and postero-lateral intra-cytoplasmic flagella, and two pairs of parabasal bodies; 14 microns. (30) Smaller, globose race of the same; 12 microns. (31) Cyst of *Waskia intestinalis*. (After Wenyon and O'Connor, 1917, pl. 4, fig. 15); 6 microns. (32) Ovoidal cyst of the same; 7.5 microns. (33) Pyriform cyst of *Chilomastix mesnili*, with cytostomal loop surrounding undulating membrane, anterior blepharoplast with rhizoplast running to nucleus and chromatin plaque; 7.5 microns.

appears to be only a single nucleus in the cysts. This is the most confusing cyst encountered in stools when spheroidal or ellipsoidal in shape, as it appears to be in some cases. It can usually be determined in heavily stained cysts in iodine-eosin stain under the oil immersion by rolling the cyst into favorable position for inspection. In pyriform cysts the wall is thickened slightly at the top. Its largest diameter is from 6 to 9 microns, thus establishing a ready basis for confusion with small ellipsoidal cysts of *E. dysenteriae* and *E. nana*. This is the most abundant flagellate cyst in human stools next to those of *Giardia*.

## WASKIA INTESTINALIS

This flagellate (Fig. 31), described by Wenyon and O'Connor<sup>1</sup> from Egypt, occurs rarely in our records. Its free state appears in liquid stools and its cysts less frequently in formed stools. Its cysts are of the same type as those of *Chilomastix* but are more slender and tapering, with the internal structure less clearly defined.

## GIARDIA INTESTINALIS

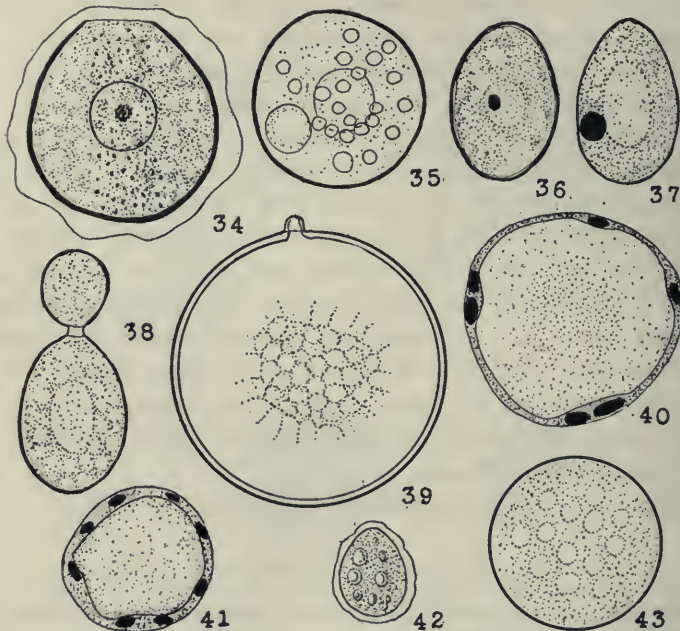
Cysts of this common flagellate (Figs. 29 and 30) occur often in great numbers and in cyclic recurrence in cases of infection. There are two races, one with a short ellipsoidal to subspheroidal cyst, about 10 to 12 microns in length, and a more common one with longer, more slender cysts, 12 to 14 microns in length. They can be distinguished very readily by their shape, their partially separated cyst wall, and especially by the two or four, usually polar, nuclei, the curved, longitudinal axostyles, and the one or two pairs of curved, comma-shaped parabasal bodies. They resist iodine-eosin stain for some time, but unevenly in different cysts, some staining dark brown rather quickly and others not at all. In destaining in iron hematoxylin these cysts usually lose most of their stain before the intestinal amebas are properly decolorized, and are often shrunken in appearance. It is not unusual to find many dead, abnormal and shrunken cysts in fresh stools which stain quickly with eosin.

Cysts of *Trichomonas intestinalis* are unknown.

## VEGETABLE ORGANISMS: BLASTOCYSTIS HOMINIS

This organism (Figs. 40, 41 and 42), next to the intestinal yeasts, is the most abundant organism here discussed. It usually accompanies other protozoan infections. In examinations of 1,120 stools with 440 infections with this organism, it occurred alone in 116 instances or 27 per cent. only. In other cases it accompanied *Giardia*, *Chilomastix*, an intestinal ameba, or some combination of these organisms. It is exceedingly variable in size, from 3 to 20 microns, and in shape, as well as in its reactions to stains. While generally spheroidal in the larger sizes the small primary stages are often ellipsoidal, thus resembling *E. nana*. The larger stages have a central homogeneous mass, highly refractive and with the optical appearances of protozoan cysts, while the peripheral cytoplasm is very transparent and may be surrounded by an unstainable, extraordinarily hyaline, mucous coat. The spheroidal central mass sometimes takes on an angular contour. The outer, granular, protoplasmic sheath stains pink in iodine-eosin stain, which brings out the refractive granules of the sheath and thus reveals the true nature

of the organism. The central area takes up little eosin. The minute primary cysts have no such central mass but granular material fills this region which takes on a yellow color in iodine-eosin stain. Their granulations and their ellipsoidal or oval shape renders them extraordinarily similar to *E. nana*. The thin pink film, visible after exposure to iodine-eosin stain, which surrounds these primary cysts (Alexeieff<sup>10</sup>) reveals their probable relation to *Blastocystis hominis*. This organism appears in literature as the cyst of *Trichomonas*.



Figs. 34 to 39.—Vegetable cysts,  $\times 2800$ . (34) Cyst of unknown affinities; iodine-eosin; 9 microns. (35) Large race of spheroidal yeast with central vacuole; iodine-eosin; 8 microns. (36) Common intestinal yeast with subcentral vacuole and lateral deeply stained granule below; iron hematoxylin; 7 microns. (37) Same with granule at the side; 7 microns. (38) Budding yeast; iodine-eosin; 7 microns. (39) Homogeneous cyst of unknown relations, yeast or phycomycete with trace of budding; iodine-eosin; 13 microns.

Figs. 40 to 42.—*Blastocystis hominis*. (40) Secondary stage with large central vacuole with homogeneous contents; 10 microns; iron hematoxylin. (41) Small stage of the same; 7 microns. (42) Minute primary stage with granular center and peripheral film; 5 microns; iodine-eosin.

Fig. 43.—Spheroidal phase of an intestinal mold; 8 microns; iodine-eosin.

There are certain large forms which are evenly and coarsely granular in the central region which then stains a dark red color with iodine-eosin stain. They appear to be forms of *Blastocystis*.

10. Alexeieff, A.: Sur les "Kystes de *Trichomonas intestinalis*" dans l'intestin des Batraciens, Bull. Sc., France et Belgique 44:333, 1911.

## HOMOGENEOUS CYSTS

In many stools there occur spheroidal cysts (Fig. 39) from 6 to 20, rarely 30 microns in diameter, which in unstained smears are sometimes brownish as though tinged by iodine or bile. They have a typical cyst wall and vary in content from a homogeneous, undifferentiated, substance resembling cytoplasm to numerous phases of vacuolation. Rarely a structure resembling a nucleus is found. It is possible that they represent degenerative phases of one or several organisms of the digestive tract or of cysts or spores habitually contaminating the food, instead of a distinct organism. The nature of their occurrence indicates a relationship to some normal inhabitant of the digestive tract. These problematical structures appear to be included in the "iodine cysts" of Wenyon and others as the "cysts without iodophilic body." The published figures of these "iodine cysts" suggest that these cysts with iodophilic body are a large race of *E. nana*. These homogeneous cysts are probably the chlamydospores of a phycomycete or resting stages of a yeast.

In iodine-eosin stain the color is intensified, but in our experience they do not contain localized glycogen or brown-staining vacuoles. Not infrequently there is a small protuberance at one point where the wall is thin, suggesting a yeast-like budding.

## INTESTINAL YEASTS

The most abundant organism here considered is an intestinal yeast (Figs. 34 to 38) normal to the human digestive tract. It occurs in practically every stool, in varying degrees of abundance. It appears, as a rule, in the form of a small ellipsoidal organism with a slightly excentric light area and adjacent granule in the granular cytoplasm and a heavy wall. It stains red promptly in neutral red or in iodine-eosin, and is thus at once separated from protozoan cysts. The yeasts are floated off by concentration methods. They are exceedingly variable in their reaction to iron hematoxylin, usually decolorizing entirely or retaining a very heavy stain. They sometimes show terminal budding (Fig. 38) or traces thereof.

In a few cases a large race or species has been found which is more resistant to iodine-eosin, simulating in size and form the ellipsoidal small race of *E. nana* and *E. dysenteriae* (Fig. 35). These float off on concentration and reveal their affinities to the yeasts in stained preparations.

## FECAL MOLDS

On stools which have stood for a day before examination, there may appear a gray coat of mold (Fig. 43), some of whose spores are confusingly similar to protozoan cysts at first glance. They are, how-

ever, more highly refractive, have heavier walls, and are often more vacuolated. An examination of the surface coating of the stool will reveal the source. The range in diameter is from 7 to 15 microns and in form from spherical to ellipsoidal, or somewhat quadrangular, and they are sometimes accompanied by elongated cylindrical sections of the hyphae. Small spherical forms found with these molds are distinguished from *E. dysenteriae* by higher refractivity, heavier cyst walls and absence of typical nuclei.

There occur erratically in stools, often abundantly, certain peculiar cysts (Fig. 34) of unknown affinities. They are about 10 microns in length, broadly ovoidal, truncate at the smaller pole, with thick-walled cyst except over the truncate area. The cytoplasm shows an axial, granular zone and central nucleus with karyosome. They are frequently enveloped in a fibrous, indefinite sheath.

It should be noted, in closing, that repeated successive examinations are essential to establish an adequate diagnosis and that flagellate infections are most readily detected in fluid stools after a saline purge, whereas the encysted phases of these and of the entamebas are more readily found in the formed stools of infected persons. The intermittent or rhythmic appearance of the encysted phases of the intestinal protozoa necessitates these repeated examinations to detect infections. Three successive examinations will detect the majority of infections revealed by cysts, and six may be considered to indicate a probable negative. Repeated examinations at intervals of several weeks are desirable in critical cases. All tests of cure after treatment should rest only on several repeated series of examinations to be conclusive.

# THE IRRITABLE HEART IN GENERAL PRACTICE

## A COMPARISON BETWEEN IT AND THE IRRITABLE HEART OF SOLDIERS \*

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During the last year or two medical literature abounds with various descriptions of the soldier's and recruit's heart. Indeed, so much has been written that with but a superficial knowledge or interest in cardiology, the impression is gained that a new and distinct entity characteristic of warfare had been discovered, and that it is never, or only extremely rarely, observed in civil life. This impression is heightened by the fact that similar conditions in civil life have scarcely been alluded to in the numerous reports, and that new and more or less confusing names have been given to this complex. To mention a few: The soldier's heart; effort syndrome; neurocirculatory asthenia; neurocirculatory myasthenia; disordered heart action and hyperthyroidism. From the broader viewpoint of clinical medicine, and as a result of an intensive study of the condition in cardiologic practice for many years, the examination of hundreds of candidates before the draft board, and a brief observation in camp hospitals, I believe the term "irritable heart," or even "cardiac neurosis" best fits the syndrome. Either appellation applies to all types of instability and irritability of cardiac innervation both in general and military practice in which there are assumed to be no organic cardiovascular changes. These terms, irritable heart and cardiac neurosis, are admittedly generic. They should be so, I believe, because the condition may have different underlying etiologic factors and varying clinical manifestations.

Perhaps, because of the early intensive cardiologic work in the present war, the fundamental relationship between the irritable "soldier's" heart and a similar condition in civil life has not been emphasized sufficiently. Various theories were at first propounded to explain its frequency in soldiers. For example, infection was assumed to play a fundamental rôle.<sup>1</sup> But the numerous cases occurring in American camps among recruits who had never seen active service and who had had no infection tended to upset this theory. The fact that

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\* Read in part before the New York County Medical Society, April, 1919.

1. Medical Research Committee, Special Report Series No. 8, 1917, Report upon soldiers returned as cases of "Disordered Heart Action" (D. H. A.) or "Valvular Disease of the Heart" (V. D. H.).

diminished blood alkalinity (acidosis) was found in a certain number of the cases studied abroad, was also given as a tentative explanation. It seems possible that in such individuals the "acidosis" and change in the buffer salts in the blood<sup>1</sup> may have been the result instead of the cause of the irritable heart because of the circulatory disturbance and consequent interference with proper elimination of toxic products.

Intensive military training has taken men from civil life without regard to their previous occupations, and has immediately exposed them to the stress, exertion and fatigue of camp life. I am not criticizing this procedure, because the exigencies of the war undoubtedly demanded haste. Besides, it may perhaps have been wise to discover as soon as possible those recruits who were totally unfit for actual war service. Concomitant with unwonted muscular exertion, especially in those from sedentary life, there is a certain amount of nerve fatigue, perhaps best expressed by the common term "fag." Nerve fatigue, psychasthenia and neurasthenia, are admittedly somewhat vague terms and are open to wide variances in meaning, but they best express a tendency to quick exhaustion, inability to properly coordinate somatic and even cerebral functions, and irritability and restiveness of these functions. This nerve fatigue and instability often characterize patients with irritable hearts. In addition, there is the important emotional factor, the mental attitude of the recruit toward war. Is he cowardly by nature? Does he fear warfare? Can the natural diffidence against war in a peace-loving people be overcome rapidly enough by instillation of the martial spirit, of military morale? Can the recruit's mind readjust itself rapidly enough to the vital necessity of risking life and limb for country? How far are such questions related to the nerve stamina of the individual? Does the recruit come of nervous stock? Has he shown any neurotic manifestations in civil life? Have venery and sex ideas played a large share in his thoughts? Questions like these undoubtedly play large rôles in the mental and nerve poise of the individual, may retard or induce, considerably influence, or even cause the advent of the irritable heart.

Such are some of the important crass neurologic and psychiatric factors in camp training. These are tremendously intensified by actual warfare and combat; the nerve tension, perhaps of weeks, before actual combat; the dread of injury or death in the clash of battle; the nerve exhaustion following it; fright in all its phases; these are here the outstanding factors.

Is there any correlation between the irritable heart under camp and war conditions, and that found in general practice? I believe the two conditions are comparable, and that its infrequency in civil life is due to the relative rarity of the factors just mentioned. Besides,

in general practice, I believe we do not delve sufficiently into possible etiologic data. We are prone to weigh the patient's story too lightly because there is no tangible corroborative physical evidence to be seen, heard or felt. Neurotic individuals, especially those with cardiac neurosis, have frequently told me that they feel anger and excitement "in the heart," while others with gastric disturbances feel similar emotions "in the stomach." It may appear unscientific to believe such statements when no method of examination is open to us to prove or disprove them, but, measured by our own personal experiences, I am sure that there are physicians who at some time, under special emotional stress, such as fright and anger, have referred their sensations to the heart or abdomen, and I need but recall poetic and romantic literature which abounds with examples of pangs of jealousy and rage being referred to the heart.

I shall now give a few examples typifying the irritable heart as observed in general practice, and shall emphasize particularly the probable underlying neurologic "insult" which initiated cardiac symptoms.

#### REPORT OF CASES

CASE 1.—J. F., aged 28, a furnace worker for years and a man of strong muscular development, had been married five months. The only infectious disease he can remember is typhoid when a child. Although continually at his laborious work, he had had slight precordial pains for some months. He cannot account for their origin. Three weeks ago, he had a quarrel with another laborer. Since then he has had a dry cough, and occasional palpitation and dyspnea. The patient has lost 13 pounds in weight since the onset of his illness.

*Examination.*—The lungs are normal. Inspection of the precordium reveals slight overaction in the mitral area. There is no precordial sensitiveness on slight or deep pressure. On auscultation there is heard a strong ventricular apical impact; the first sound is somewhat like a thrill and split in character. The other sounds are normal. The pulse rate varies suddenly from 72 to 100 per minute. This increase is not always caused by exercise. When the heart beats at the higher rate, it can be slowed considerably by having the patient take a deep breath and holding it for several seconds. The thyroid is not enlarged. The systolic blood pressure is 142; the diastolic, 70. The urine is normal. There is no edema of the legs. The knee reflexes are very lively. The cardiac outlines, as shown by the orthodiagram, are normal; the fluoroscope shows definite overaction of the aorta and pulmonary artery.

This patient presented no evidence of organic cardiovascular disease. A dispute with a fellow laborer had apparently aggravated a dormant cardioneurotic condition, and produced hyperexcitability of the cardiac nerve mechanism, with consequent sudden rapid rhythm and the uncomfortable sensation of palpitation. I advised the patient to give up his work for a week or two, not because I feared the effect of work upon his heart, but for purposes of mental rest and relaxation. Bromids in moderate amounts were also advised. I

have since heard from the family practitioner that the patient followed directions and that he is again at work and feeling well.

CASE 2.—J. R., aged 27, unmarried, a grocer, stated that he had had occasional precordial discomfort in lifting heavy boxes. This, however, never interfered with his activities until five years ago. He then had an attack of severe abdominal colic and felt faint. His heart action became rapid. The doctor who treated him at that time stated that the heart action was regular, the rate 180 per minute. Since then, any excitement, undue mental strain, attempts at hard work, or even full and hearty meals are accompanied by rapid heart action and precordial pains. His appetite is good, he has not lost weight. He has become introspective about his heart, the more so since he has been drafted and accepted for military service. There is no history of any previous infection.

*Examination.*—The patient is robust and well nourished. The thyroid is not palpable. The systolic blood pressure is 110; the diastolic, 90. Inspection of the chest reveals slight apical overaction. On palpation, there is a thrill-like systolic shock at the apex. There is no precordial pain or sensitiveness to superficial or deep pressure. At the apex, the first sound is strong and is so broken up or split as to give the impression of a thrill; the other cardiac sounds are normal. The orthodiascopic tracing shows a somewhat enlarged pulmonary artery; the other cardiac curves are normal in shape and size. The abdominal examination presents nothing abnormal. There is no edema of the legs. The urine is normal. The knee reflexes are somewhat exaggerated. When at rest, the pulse rate is 100 per minute; the rhythm is normal. After moderate exercise—for example, walking 100 feet fairly rapidly—the rate rises to 150 per minute; the patient then complains of some dyspnea and precordial distress. After three minutes rest, the pulse rate returns to its previous level.

The original “insult” was an attack of paroxysmal tachycardia following severe abdominal colic. Prior to that, he was a hard working individual whose only complaint was the not unusual one of precordial distress from heavy lifting. The original paroxysm of tachycardia has left the cardiac mechanism hyperirritable, so that undue excitement or moderate physical exertion caused rapid heart action with dyspnea and precordial pain. Despite the physical signs over the mitral area on palpation and auscultation, I believe that organic disease can be excluded. I have found identical signs, a thrill-like broken systolic shock on palpation, and a thrill-like broken and strong systolic first sound in a number of recruits of the draft age in whom, after exercise, cardiac action was accelerated or over-forceful.<sup>2</sup> Such abnormal signs are not evidence of organic disease in these individuals, for when the cardiac rate or overactivity can be controlled, as, for example, by having the patient breathe slowly and deeply, the abnormal signs become less marked or even disappear. There was nothing in the patient’s previous history, neither rheumatism nor other infection, which could be correlated etiologically with pathologic damage to the heart.

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2. Neuhoof, S.: Cardiovascular Examinations of Draft Candidates by the Local Boards, N. Y. Med. J. **107**:411, 1918.

CASE 3.—L. R., aged 48, married, salesman, has always been very active and athletic, but of neurotic temperament. He had palpitation when 20 years old. He frequently suffers from cold hands and feet. For several months he has had frequent quarrels with his wife. The chief cardiac symptoms are sudden, momentary palpitation, especially at night, and clammy hands and feet. He is now afraid to exercise because he believes he has heart trouble. He never has any dyspnea while at his work. His family physician states that he has an occasional dropped beat (extrasystole) and that he has an occasional hyaline cast in the urine.

*Examination.*—The man is of athletic build. The systolic blood pressure is 118; the diastolic, 95. His hands and feet are cold, clammy and wet with perspiration. The pulse is regular; the rate, normal. The heart sounds are normal. There is no precordial sensitiveness. Rapid walking does not abnormally increase the cardiac rate; after two minutes rest, the rate reaches the normal. The orthodiascopic tracing shows an aorta of normal size and contour. The heart is not abnormally large for a man of his physique. The knee jerks are lively. There is no edema of the legs. The urine contained no albumin, sugar or casts. Although there was no arrhythmia during the examination, the physician's observation and the patient's statement make it probable that the "palpitation" is due to occasional extrasystoles. The instability of the vasomotor system—sweating and clammy extremities—was the most prominent phenomenon.

The etiology of the cardiac and vasomotor symptoms was quite evident, family nagging in a neurotic individual. This fact also accounted for the attacks at night. During the day his mind was occupied with his work; in the evening and at night came the irritation and time for introspection. The etiology naturally suggested the remedy. First, the absolute assurance to the patient that his heart was normal. As proof of this he was advised to continue his athletics and business. Second, avoidance of family quarrels. The patient was also given 30 grains of mixed bromids at night and 5 grain of the extract of suprarenal gland, the latter to be taken when the vasomotor and cardiac symptoms were particularly prominent. The attack ceased after several days; he was soon able to take up his business and athletic activities.

CASE 4.—H. M., aged 26, unmarried, theatrical manager, gives a questionable history of rheumatism in childhood. His mother has hypertension and is extremely neurotic. As a college student he had always been well, was fond of athletics and never had any cardiac symptoms until five years ago. He was then a helpless eye witness to the drowning of his brother. He became hysterical and was confined to bed for two weeks with hysterical attacks. Soon thereafter, and for two or three years, he had nervous indigestion; the chief symptom was belching. The gastric condition improved under treatment. He then developed cardiac symptoms; these consisted of palpitation and of pain in the left chest, particularly after excitement. After walking a mile now, he becomes "tired all over." He has recently been told by a physician that his heart is occasionally irregular. He is a very rapid eater. His business as theatrical manager leaves him no time for relaxation.

*Examination.*—The thyroid gland is not enlarged. The systolic blood pressure is 120; the diastolic, 60. There is slight carotid hyperactivity and slight exaggeration of the apical impulse. The sounds at the base are normal. The first sound at the apex is normal; it is immediately followed by a sharp, super-

ficial click which is transmitted somewhat to the left; it disappears on deep inspiration. There is an occasional superficial pleuropericardial rub to be heard in this region. There is no precordial sensitiveness. The pulse rate is normal; rapid walking produces no dyspnea and only slight acceleration of the cardiac rate. The orthodiascopic tracing shows a heart of normal size and contour, the ventricular contractions are very vigorous. The examination of the abdomen presents nothing abnormal. There is no edema of the legs. The knee reflexes are very lively.

I believe that the adventitious sounds at the apex are due to an old pleuropericarditis and have no relation to the patient's symptoms. The demeanor and action of the patient during the examination were those of an individual who is hyperactive and excitable. Whether this nervous instability antedated his brother's drowning, or whether the latter only intensified an inherent tendency, I cannot state because of insufficient data regarding his early life. The history leaves no doubt that the original hysterical attack was the starting point of a train of nervous symptoms which first affected the stomach and later the heart, producing the subjective feeling of palpitation and precordial discomfort. The symptoms were present despite the fact that the cardiac rate was normal and was not inordinately increased by exercise; this phase of the symptomatology will be discussed later.

The question arises, would such a patient make a good soldier? I do not believe that the pleuropericardial sound should invalidate him from military duty. Since there is no tachycardia following effort, the fundamental question is the psychologic one of his attitude toward the war. If properly patriotic, camp life with its release from the type of hurried and harried life he had been leading, would probably cause a trend toward a normal, physiologic level, and his cardiac symptoms would cease. I have since heard that he entered the army and developed no further cardiac symptoms.

To show that the irritable heart in women may resemble those found in men, I have added the following two cases:

CASE 5.—Mrs. W., aged 52, has had five children and several miscarriages. The menopause occurred two years ago. At that time she had occasional slight flushes for two months. Ten years ago she had gallstone attacks for which she was treated in Carlsbad. She has had no attacks for several years. Her husband died suddenly in bed two years ago. She was very much upset by his unexpected death. Since then she began to have palpitation, especially at night, and dreaded going to bed for fear that she too might die suddenly. She also had palpitation when excited or when walking in the street. This was accompanied by sharp substernal pain, which occasionally radiated to the left arm. The systolic blood pressure taken at different times varied between 180 and 200. She had been told that she has, and she has been treated for, hypertension and arteriosclerosis. She had been on a rigorous diet; and although often hungry, accompanied by faintness and tachycardia, she was afraid to eat because of the fear of increasing the blood pressure.

*Examination.*—The patient, a stout woman, is not dyspneic while at rest. The thyroid gland is not enlarged. The systolic blood pressure is 150, the diastolic 100. There is some overaction of the carotids and aorta. There is no pain on superficial or deep precordial palpation. There is a strong systolic impact felt at the apex. On auscultation all the cardiac sounds are normal. There are no murmurs or accentuated sounds. When at rest, the cardiac rate is 110; it is slightly decreased on deep quiet inspiration. Walking causes a cardiac rate of 120 per minute; after a few minutes, it drops to 110. There is no edema of the legs. The urine and knee reflexes are normal. The orthodiascopic tracing shows a heart of normal size and form. The electrocardiogram shows nothing abnormal.

In spite of the history of hypertension and of precordial attacks, I regarded the case as one of pure cardiac neurosis due to fright, reflexly aggravated by hunger pangs; the latter was due to a starvation diet which kept the stomach empty a good part of the time, and probably induced gastric hyperperistalsis. I allowed the patient a liberal, mixed diet, to be eaten at regular intervals. She was given bromids at night, and 5 grain tablets of the extract of suprarenal gland for the attacks of tachycardia. Within three weeks her condition improved remarkably. The systolic blood pressure was 130; the precordial pains disappeared; the cardiac rate fell to 80 per minute. The patient slept well at night. She walked regularly in the open without discomfort. Reassurance doubtless was a large factor in the improvement.

CASE 6.—Mrs. G., aged 26, has been married one year. She has a baby three months old. Seven years ago she had a love affair; she became disappointed in her lover and gave him up. She then had many hysterical spells, finally culminating in attacks of severe nocturnal dyspnea. Since then she has had many such attacks. While pregnant the attacks ceased entirely, but they have recurred recently. Her home life is a happy and comfortable one. During a typical attack, her hands and feet become cold; the heart action, rapid; she becomes dyspneic, there is a feeling of palpitation and of abdominal pressure; accompanying the latter is intestinal hypermotility and rumbling. The patient says she tries to control the attacks, which usually come on and are severest at night. She is losing weight and fears going out because of the attacks. Her appetite is poor.

*Examination.*—The teeth and tonsils are normal, the thyroid not enlarged. During the examination, her hands become cold and clammy. The patient stated that she was having a mild attack. Inspection of the cardiac area was normal. There was a broken, thrill-like systolic shock palpable and a thrill-like first sound heard over the mitral area. The other heart sounds were normal. The cardiac rate was 110 per minute; slight exercise (walking in the room) brought the rate to 120 per minute. At the end of the examination, the rate was 100 per minute. The abdomen presented nothing abnormal. The knee reflexes were very lively. There was no edema of the legs. The orthodiascopic tracing showed a heart normal in size and shape.

This is an excellent example of a heart made irritable originally because of an emotional strain sustained years ago. The symptoms subsided during pregnancy, apparently because the pregnant state caused a profound change in her mental attitude, a common result

of pregnancy. A hyperfunction of one or more of the endocrine glands may have been the fundamental cause of such change. After pregnancy, there was a recurrence of the old symptoms, vasomotor instability and dyspnea were the chief of these. Rapid heart action in itself can cause dyspnea. The presence of vasomotor symptoms, due to irritability of that center, seems to indicate in addition the possibility of hyperexcitability of the respiratory center. Studied with a respiratory apparatus such patients may be found to be suffering from tachypnea, rather than from dyspnea.

A review of the few examples given, as well as of the vast majority reported in the literature, shows that the salient feature of the symptom complex of the irritable heart has been instability of the vasomotor or of the accelerator mechanism, or of both. I believe that all the symptoms, as well as the abnormal physical signs, are derived from these fundamental disturbances. Giddiness, flushes, pallor, dermatographia, swooning, fainting are evidently due to vasomotor disturbances. They are found very frequently, for example, in many types of gastric disorder without cardiac symptoms. The tachycardia in irritable heart ranges from simple pulse acceleration to gradual or sudden, sharp increases in rate following exercise, emotion or unknown causes. To use a simile derived from physiology, the threshold for the abnormal excitation varies considerably. The cause of the various types and degrees of precordial sensation, such as heaviness, pressure, pain, skin and deep sensitiveness, is still obscure because nerves of sensation have not been discovered in the heart and the reflex arcs involved are still matters of surmise. But the clinical fact, already alluded to, that some people in anger or fright refer the first sensation to the heart, and Head's theory of sensitized spinal segments, indicate how a diseased or improperly functioning organ can cause various local referred sensations.

The abnormal physical sign of irritable heart to which most importance is attached, is a thrill-like palpable systolic impulse and the thrill-like, split, or broken first sound at the apex. Soft apical murmurs that are not transmitted, slightly accentuated second pulmonic sounds, and the occasional reduplicated second sound over the pulmonary artery, the aorta or at the apex, may be dismissed because they are not characteristic of the irritable heart and are sufficiently common in other conditions. When present, the thrill in the irritable heart with tachycardia is systolic in time; its degree and transmission seem to depend on the violence as well as the rapidity of the heart action. A thrill, for example, is infrequent in the rapid regular heart action of paroxysmal tachycardia, in which the heart beats at the rate of from 150 to 200 per minute. It is quite common, however,

in exophthalmic goiter, even when the cardiac rate is as low as 100 to 110 per minute. I believe it is the violence of the heart action, rather than its rapidity, that accounts for the abnormal systolic thrill, for theoretically, at least, it seems probable that blood, suddenly and forcefully ejected by ventricular systole, can produce impinging counter-currents and whorls against the inner ventricular surface, which, to the ear and touch, are interpreted as broken, almost cog-tooth-like interruptions of the normal systolic sound and thrust. This receives some support from the observation I have frequently made that if the cardiac rate and hyperactivity can be controlled, as is frequently the case, by having the patient take a long, deep breath and holding it a moment, the thrill often diminishes or disappears, almost commensurate with corresponding decrease in ventricular hyperactivity.

I believe I have shown a close etiologic and symptomatic relationship between the irritable heart in general and military practice. In the latter, tachycardia, especially following effort, is the most common sign; vasomotor symptoms alone are less common, while in general practice, the vasomotor symptoms often predominate. It must be remembered and emphasized that patients frequently complain of palpitation without tachycardia, that is, they have a subjective feeling of palpitation. In a few instances, I have been able to discover with the aid of the fluoroscope that such patients showed particularly strong ventricular contractions; the left ventricle was decidedly diminished in size with each systole. This may perhaps be the physical explanation of subjective palpitation in some of these cases.

I have tabulated a list of the commoner symptoms, physical findings and etiologic factors as I have observed them in the neurotic heart in general practice, and have arranged each column, as far as possible, in the order of the importance of the various factors.

#### IRRITABLE HEART IN GENERAL PRACTICE

Symptoms	Physical Findings
Abnormal precordial sensations (pain, sensitivity, oppression)	Normal sized heart; thrill-like, split systolic impact and first sound over the mitral area
Vasomotor symptoms (giddiness, flushes, dermatographia, faintness)	Systolic murmur over lower precordium; rapid regular heart
Dyspnea (actual and subjective).....	Normal rate with occasional extrasystoles
Extrasystoles producing subjective sensations	Sudden changes of heart rate
Tachycardia following slight effort.....	Slow heart action with powerful ventricular contractions
Constant tachycardia	
Sudden changes of heart rate	
Etiologic Factors	Therapy
(Causing hyperirritability of the sympathetic system):	Reassurance
Previous history of shock, fright or emotional strain	Short rest
Reflex excitation from gastro-intestinal canal.	Retraining, especially through graded games
Physical fatigue with insufficient rest.....	Bromids in the beginning or in severe cases
Insufficient recuperation following acute infections	Suprarenal gland extract (especially for vasomotor symptoms)
Disturbance of the organs of internal secretions (thyroid? adrenals?)	

Some of the headings require additional comment; others have been discussed in the description of the case histories or otherwise.

Dyspnea, as stated, may be actual, e. g., in patients who develop tachycardia as the result of exercise. At other times, especially in patients with vasomotor symptoms, the dyspnea seems purely subjective, for there is no increase in the rate or depth of the respiration. In rare instances, tachypnea — rapid breathing — results.

The size of the heart, as mapped out by ordinary methods of clinical examination, gives the impression of enlargement. This impression, however, is the usual one in almost all cases of violent, rapid heart action. I have had occasion to fluoroscope many cases of tachycardia that had no organic cardiac disease. In every instance, I made orthodioscopic tracings, an exact method of delimiting the cardiac area, and I was not able to demonstrate any characteristic change from the normal in the size or configuration of the heart. I have not measured the breadth or other cardiac diameters according to the somewhat popular standards of Dietlin and Groedel, because these standards apply chiefly to those of normal physique. This physique approximates the normal in soldiers, hence standardized measurements may be of some value in them. But I have frequently found the standard (a transverse diameter of 11 to 13 centimeters) too small, especially in those whose diaphragms are high and not very mobile. In these individuals, the ventricular surface lies abnormally flat along a disproportionate part of its length, hence the resultant breadth is larger than the standard, although the organ is not actually enlarged. On the other hand, I have only rarely found the drop or pendulous heart, that is, a narrow organ resting lightly on the diaphragm along a small part of its under surface.

Among etiologic factors of the irritable heart, I have mentioned, as a fundamental factor, an "emotionally unstable, neurotic individual" (see table). Some of the patients give definite histories of a nervous taint in either parent, or in a closely related member of the family. I believe, however, that while such taints may be common, they are not the actual exciting or impelling causes of the neurotic heart. Some great emotion, fright, dread, shock, is usually the directly antecedent cause of the outbreak of the cardiac symptoms. Reflex excitation from the gastro-intestinal canal is the next most frequent. In other words, the cardiac nerves of an hereditary neurotic individual apparently react more readily, more continuously and in a more exaggerated fashion to a neurogenic "insult" than do those of an individual with normal poise.

## CAUSE OF IRRITABLE HEART

Having described some illustrative cases and sketched various symptoms, physical findings and etiologic factors, the question arises is there some basic underlying excitation to account for the irritable heart? Careful analysis of all the various phases of the irritable heart, especially facts elicited by a careful history, lead me to the belief that it is probably fundamentally due to hyperexcitation of the sympathetic nervous system. In his classic paper on the irritable heart of soldiers, Da Costa<sup>3</sup> ascribes many of the symptoms to stimulation of the sympathetic system. Recent observations of the same subject show that there exists hyperirritability of the accelerator reflex arc<sup>4</sup> and probably also of the vasomotor mechanism.<sup>5</sup> No diminution of the vagal tone was found, as judged by atropin experiments. Experimental observation demonstrates that fear and dread in cats, for example, is accompanied by erection of the fur, by exceedingly rapid heart action, by profuse perspiration and by staring eyes. These are all apparently due to hyperexcitation of the sympathetics. Such symptoms have their analogies in man. Fright and terror can be the immediate cause of exophthalmic goiter. Authentic cases of this type have been reported. I myself have observed at least two such undoubted cases. One of these was that of a young girl, who, while riding in a passenger elevator, saw a man killed before her eyes. On reaching home, she went to bed with rapid heart action, and within a few weeks, developed all the classical signs of exophthalmic goiter. In recruits, the development of typical exophthalmic goiter has been observed occasionally. On the other hand, the development of rapid heart action, tremor and the other signs and symptoms of the irritable heart, without the type of goiter found in exophthalmic goiter, has been regarded by some as evidence of hyperthyroidism.<sup>6</sup> Some of these individuals had soft goiters. But changes in the thyroid, especially cystic degenerations, are by no means accompanied regularly by cardiac or nervous symptoms. The subject of hyperthyroidism brings up for discussion the moot and involved question of the endocrine glands. Are we justified in assuming hyperthyroid activity without the typical eye and thyroid signs of exophthalmic goiter? I do not believe that the present state of our knowledge allows us to go thus far. Besides, I think that the symptoms of hyperthyroidism,

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3. Am. J. Med. Sc., January, 1871, p. 40.

4. Cotton, Rapport and Lewis: Observation on Atropin, Heart 6:295, 1917.

5. Cotton, Slade and Lewis: Observation on Pilocarpin Nitrate, Heart 6:299, 310, 1917.

6. Brooks, H.: Hyperthyroidism in the Recruit, Am. J. Med. Sc. 156:726, 1918.

so-called, can be understood better and more rationally on the broader and more fundamental basis of hyperirritability of the sympathetic system. It is possible that this supposition may even explain why some cases of irritable heart develop all the classical signs of actual exophthalmic goiter, for the endocrine glands themselves, especially those endowed with a rich nerve supply, are presumably subject to varying influences of nerve excitation and tone. This has been proven experimentally for the suprarenals. The entire subject is further complicated by the probability that the endocrines themselves are mutually influenced through the action of hormones. This was illustrated in a case I saw at one of the camps in which the development of a constant tachycardia was one of the prominent features. The man had gained about 50 pounds in weight within a few weeks; his breasts had taken on female characteristics and sexual desire had disappeared entirely for several months. The thyroid was not enlarged; there was no exophthalmos nor tremor. Despite the rapid heart action, he looked the typical example of hypopituitarism. According to the present terminology, the case would probably be classed as dyspituitarism.

Hyperexcitation of the sympathetic system can undoubtedly produce rapid heart action, tremors and sweating; and, as already stated, symptoms starting thus, may, in some instances, finally eventuate in actual exophthalmic goiter. In several polygraphic tracings of undoubted cases of exophthalmic goiter, I observed that the conduction time from auricle to ventricle (the *a-c* interval) was diminished even when tachycardia was not marked.<sup>7</sup> This fact may offer some clinical corroboration of the experimental observation<sup>8</sup> that one of the effects of stimulation of the sympathetic is a decrease of this interval. Only recently<sup>9</sup> it was pointed out that the thyroid is subject not only to hyper- and hypo-, but also to dysfunctions, a fact which may account for some of the vagaries and apparent contradictions in the clinical syndrome of exophthalmic goiter.

The physiologic antagonism between the sympathetic and vagus systems, between the accelerators and inhibitors is, of course, well known. In an abnormal antagonism between these two controls, I believe that even when inhibition is normal, its power can be nullified by hyperirritable and hyperactive accelerators. In other words, the inhibitory tone, as tested by atropin, may be normal, yet its power

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7. Neuhof, S.: *Clinical Cardiology*, pp. 55, 104.

8. Rothberger, C. J., and Winterberg, H.: Ueber die Beziehungen der Herznerven zur Form des Electrocardiograms, *Arch. f. d. ges. Physiol.* **135**: 506, 1910.

9. Janney: *Arch. Int. Med.* **22**:187, 1918.

can be nullified by hypertonic accelerators. This is perhaps explicable by the physiological fact that, tested electrically, there is normally no quantitative relationship between these two systems. Sympathetic hyperexcitation, therefore, can apparently upset the nice balance of cardiac nerve control, with consequent instability or lack of the normal inhibitory process.

May we not, therefore, infer that the irritable heart is due fundamentally to sympathetic hyperexcitation, unopposed or insufficiently opposed by the inhibitory apparatus, and that therefrom arises the cardiac syndrome, with vasomotor symptoms, mild tachycardias and palpitation, with and without effort, as one extreme, and the actual goiterous heart at the other?

The fact I wish to emphasize is that the soldier's irritable heart is no new complex, but is the same syndrome seen in civil life, intensified and multiplied by training and war conditions. Suspense and fright intensify latent and dormant symptoms and tendencies and cause nervous instability in those temperamentally unfit, by heredity or otherwise, to "carry on."

The treatment abroad of the soldier's heart had narrowed itself to a comparatively short period of rest and then graded restraining in camp routine, mild exercise at first, route marches, light packs, heavy packs, etc. In this way a fair percentage of these soldiers become fit for active duty. Digitalis was not found to be of any value, as indeed was to be expected, for the patient did not suffer from decompensation, nor was there any evidence of organic, valvular or muscular disease. At the beginning there had been no attempt to attack the problem of the irritable heart from the psychologic or psychotherapeutic viewpoint. Mental and physical relaxation, especially in the form of games, and later sports, was not then attempted. More recently, especially in the United States, games and farming have been used therapeutically. In private practice, where these matters can be individualized better, I have found that, if after a careful examination, patients could be assured that they had no heart disease, and that all the symptoms were the result of "upset nerves," the cure was tremendously hastened. An explanation, especially to intelligent patients, which is not too scientific, but which offers a sufficient cause for the symptoms, is also of distinct benefit. What patients dread most is sudden death; with a satisfactory explanation for their symptoms, they are usually relieved, sometimes permanently, of this fear. For the purpose of mental relaxation, as well as gradually increasing the amount of exercises, I have suggested billiards, croquet, bowling, golfing, light farming and, in cases that are improving, rowing and even swimming in shallow water. Reeducation of the tone of the

cardiac nerves in order to regain stability is oftentimes a slow and tedious process. Sudden sharp exercises should be avoided. The doctor should never omit praise, even exaggerated praise, for good work done on the patient's part in overcoming his timidity to exercise, and especially in continuing exercise and play, despite the presence of minor symptoms, such as moderate tachycardia and slight precordial pain.

Medicinally, I have found mixed bromids and suprarenal gland extracts the best drugs. The bromids given in large doses at first, lessen mental irritability and anxiety. My usual procedure is to give 1 gram of the mixed bromids, well diluted in water, three times a day after meals. Depending on the progress of the case, the dose is correspondingly diminished and finally stopped. In cases that are annoyed by sleeplessness, I add 10 grains of chloral hydrate or 8 grains of veronal every night for a few nights. I have seen no bad effects on the heart or the individual from these procedures. The suprarenal gland I prescribe in 5 grain tablets, to be taken only when symptoms, such as tachycardia or precordial distress become annoying. Paradoxical as it may seem, I prescribe this extract even when hypertension is present. Its beneficial effect seems to depend on its power to stabilize temporarily and decrease vasomotor instability by its action on the vasomotor center; it thus counteracts the cause of many of the symptoms. The effect of the drug is only temporary, hence with recurrence of the symptoms, the dose may be repeated, if necessary, several times a day.

#### SUMMARY AND CONCLUSIONS

The irritable heart as observed in general practice is similar to that found in soldiers. Vasomotor symptoms are more pronounced in the former. The etiologic factors are similar, but because of training and war conditions, dormant and latent neuroses crop out oftener and are more readily evoked; consequently the cardiac syndrome is more violent and lasts longer. Infection is a factor only in so far as it induces and produces nerve and muscular fatigue and psychasthenia. There is no pathologic change in the cardiovascular system. The fundamental cause of the cardiac neurosis with its various manifestations, seems due to hyperexcitation of the sympathetic nervous system.

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## DURATION OF NORMAL CONVALESCENCE

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BALTIMORE

These notes on the duration of normal convalescence are the result of work that was primarily designed for the treatment of war casualties, especially those resulting from gas inhalation. It was hoped to reduce the period of convalescence for gas cases and to avoid the relative frequency of effort syndrome so conspicuous in the British army. In reviewing the first five thousand case histories, which are to be the basis of a report on the functions of convalescent camps, a sufficient number of different cases were found to warrant deductions and suggestions as to the optimum duration of the convalescence from peace time surgical and medical affections. Many of the neurasthenias and anxiety neuroses follow operations or acute infections, where the patient is allowed to return to the wear and tear of the usual activities of life after a relatively short period. It may well be that the prolongation of convalescence, with graduated exercises, which proved so beneficial in the case of physical injuries, will minimize the exposure to psychic trauma during that period, and thereby prevent the outspoken mental symptoms which are apt to follow, especially in those individuals whose psychic resistance is below the normal. The daily life of soldiers subjects them to strain and to labor more intense than that to which civilians are commonly exposed, so that the recovery to normal demands the attainment of a higher standard than is sought in civilian practice. However, one is concerned with the recovery of what was lost by sickness, and in that sense the results are comparable with peace time conditions.

The camp in question was the convalescent section of a group of base hospitals which had a total capacity of fifteen thousand beds, the camp maintaining two thousand patients. These hospitals were about 50 miles from the front, and, in times of stress, became evacuation centers where patients stayed but a few days on their way further back. But in the main, the soldiers, especially those with complaints such as are met with in daily life, were treated and then discharged to duty, reclassified, or sent to the camp for convalescence or protracted observation.

The underlying principle of the camp was the retraining, by graduated exercises, of soldiers who were on their way back to the front lines — a training point and not a hospital. It was essential to insist on military discipline in order that the men, on their discharge, should be mentally, as well as physically, qualified for their normal duties. A suitable amount of relaxation was afforded by games, moving pic-

tures, theatricals, etc., which filled up practically all the time not devoted to the setting-up exercises, squad drills, hikes and fatigues — the whole being under medical supervision. The food was consistently good and abundant, and the sleeping accommodations were fair — tents for the most part, well drained and with canvas floors. The work was done during the past summer and fall, so that no allowance need be made for the cold of winter. In general, the convalescence of the patients was favored by the local conditions.

On admission and discharge, a physical examination of the stripped patient was made in all instances, and promotion through the three classes, representing increasing physical demands, was dependent on the ability of the soldier to perform the work and play of the particular class without untoward symptoms. A small but satisfactory camp hospital, with access to the laboratory of the center, made possible a careful study of the individual during his stay.

The first qualification for discharge to full duty was the promotion of the patient through the two earlier and easier classes and his ability to accomplish the daily class work of Company Three — forty minutes of steady setting-up exercises, an hour of squad drill and a 5-mile hike. If there were no contraindications, the patient was stripped and examined and then sent with his notes to the writer for a final check. How much better than the customary manner of feeling the pulse, palpating the wound, listening to the heart, telling the patient to be careful, and sending him from the ward to full duty! By the observation in the camp, his tolerance for exercise was known, and the patient himself knew what he could do.

A further very important point was realized at the camp. On discharge, the patient was fresh from drill and military discipline, which enabled him to rejoin his outfit and to take his normal place among his companions. He had recovered from the great loss of discipline that is bound to occur in the base hospital, and he had been led back into the normal routine of a soldier's life.

In order to confirm the results, a "follow-up" system was instituted. Letters of inquiry were sent to the different battalion medical officers two months after the soldier had been returned to his organization. (If the war had continued, a second letter would have followed after six months, and a third after a year.) The answers to these questions as to the patient's condition were most convincing. To date, about two thousand of these letters have been returned, thanks to the cooperation and interest of the regimental surgeons, and in more than 99 per cent. of the cases, the patients discharged to Class A, who had not been killed, wounded or gassed, were fulfilling their normal functions. And those reclassified to lower categories were doing the work of their grade.

In order that the duration of stay in camp might not be unnecessarily prolonged, all patients were seen daily, after their drill, by medical officers. Thus, men who were in good condition on entry to the camp were discharged three days after admission, the minimal time consistent with their promotion through the three classes.

To compare the duration of hospitalization of patients passing through the camp with those discharged directly to duty and not tested for their physical tolerance, a group of records was obtained from the hospital center of the period before the adoption of the convalescent camp, and before the rush of wounded and gassed necessitated rapid evacuation. These averages represent the periods which different physicians thought sufficient for recuperation. No follow-up system had been instituted for these patients, so that their final disposition is uncertain. But the writer, while working in a base hospital, has seen some of those discharged return to the hospital for relapse, weakness, painful wounds, or inability to keep up. In addition, after longer intervals, some of those previously discharged patients returned with functional mental disorders, whose precipitating trauma dated from their original entry. In the early method of handling patients, the initial stay in the hospital was sometimes proved to be insufficient, but as relapses were treated as new admissions, a false idea was obtained as to the total time lost. Transportation in France was always difficult and very slow, and any reduction in its use was well worth while.

The following tables show the average duration of stay in hospital and camps under the two systems. The first group, with the number of patients on which the average was computed, comprises those who were discharged to duty before the existence of the camp. The second group, with its larger number of cases, shows the number of days that the patients were in the hospital, plus their stay in camp. In this collection, cases complicated by secondary or intercurrent diseases are omitted.

In looking over these tables, certain suggestive observations can be made. In the first place, it is important to learn that in practically every type of disease studied, the period necessary for resumption of normal function is definitely longer than was allowed at the base hospitals.

The influenza group, which included slight colds, fever of a few days' duration, or malaise of sufficient intensity to warrant the evacuation of the patient from the front line, is the only one to show approximately equal periods. The majority of these soldiers were fit for duty on their arrival at camp, where three days were necessary for the completion of their course of work, so there is an apparent agreement in the two series. But attention should be called to a fact, not evident in dealing with averages, that a great many of the patients who came

TABLE 1.—MEDICAL CONDITIONS

Diagnosis	Number of Cases	Average Stay in Hospital, in Days, Patients Not Going to Camp	Number of Cases	Average Total Stay in Days in Hospital and Camp
Influenza.....	27	25	828	31
Pneumonia.....	24	35	170	58
Acute bronchitis.....	33	24	233	36
Mumps.....	20	18	53	39
Measles.....	0	0	18	27
Scarlet fever.....	8	57	7	77
Catarrhal jaundice.....	1	17	7	38
Diphtheria.....	0	0	5	57
Tonsillitis and sinusitis....	34	19	90	34

TABLE 2.—SURGICAL CONDITIONS

Diagnosis	Number of Cases	Average Stay in Hospital, in Days, Patients Not Going to Camp	Number of Cases	Average Total Stay in Days in Hospital and Camp
Hemorrhoidectomy.....	21	20	25	45
Herniotomy.....	31	24	41	50
Hydrocelectomy.....	6	22	7	54
Tonsillectomy.....	10	20	8	37

TABLE 3.—WAR CASUALTIES

Diagnosis	Number of Cases	Average Stay in Hospital, in Days, Patients Not Going to Camp	Number of Cases	Average Total Stay in Days in Hospital and Camp
Gas.....	214	25	1,195	37
Enteritis.....	4	14	512	30
Concussion.....	6	25	192	45
Exhaustion.....	0	0	80	40

to the camp in the late fall, when true influenza was prevalent, were held in camp for long periods—two to four weeks—while their stay in the hospital had been only a few days. It was in this group that a great many of the effort syndrome cases were found, necessitating slow promotion. In all the other groups the figures make obvious the need for a much longer period of convalescence than was generally employed. It is interesting to learn the results in the infectious fevers. Physicians do not appreciate that the average case of mumps will not entirely have recovered until over five weeks after the onset of the disease, that the duration of the average pneumonia, including convalescence, will take over eight weeks, and scarlet fever over eleven weeks. Leaving out the possible relationship between the lack of proper care during the period of convalescence and psychic trauma, one cannot but consider the danger associated with a lowering of bodily resistance to other infections—to tuberculosis and to cardiac

infections, for instance. There may be some ground for the routine questioning of patients as to the infectious fevers of childhood, especially in the presence of an unexplained cardiac lesion, a mitral stenosis accidentally discovered, or a myocarditis without determinable etiology. May it not be that the frequency of these lesions might be materially reduced by a more careful treatment during convalescence?

Consider the group of tonsillitis and sinusitis. Most patients suffering from one of these infections are out of bed and back at their daily work after a week or ten days, whereas, in the case of these young soldiers who were in the best physical condition when they contracted the disease, it appears that the normal strength is regained only five weeks after the onset of the infection. Are we not, in our daily practice, taking risks greater than we have fancied? May not the neglect of proper care during convalescence be a source for development of more serious disease?

Similar reflections arise from a consideration of the records of surgical conditions. The average herniotomy needs several weeks of care before the patient is normal again, instead of the three and a half that are commonly allowed. So often one hears that some particular surgeon can get his patients who had simple cases of appendectomy out of bed and back to work in some phenomenally short time. Is that to his credit?

In the same way, it is conspicuous that the uncomplicated tonsillectomy requires over five weeks for complete convalescence. Certainly, the majority of patients do not allow themselves so long a vacation in general practice, nor do surgeons advise so long a period.

The results obtained seem definite as to the period required for complete convalescence. And it should be emphasized that the existence of a routine of graduated exercises and military discipline favored and hastened convalescence. It was the general rule that the patients clamored to get back to their organizations where their friends, accumulated pay and mail awaited them. For these reasons and from an acquaintance with the American "doughboy" it is hard to conceive that even a subconscious desire to remain out of the fighting could have protracted their convalescence in more than a very small percentage of cases. The medical supervision was real, and both the doctors and the ward masters soon became adept in handling the occasional malingerer.

This article is presented to the attention of physicians because it is believed to be the first direct attempt to employ actual physical tests for the determination of the optimum period of convalescence, and because the periods determined seem so much longer than are generally employed.

# THE URIC ACID CONTENT OF THE BLOOD COMPARED WITH THE RENAL DIETARY TEST

THE BLAND DIET COMPARED WITH THE ORDINARY TEST DIET \*

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During the past three years we have carried out about 180 renal dietary tests and blood analyses. Most of the cases were diagnosed nephritis or arteriosclerosis, though a number of other diseases have been included in the tables. The routine employed was as follows: The blood for analysis was collected before breakfast. The patients were in bed during the dietary test. They received a uniform quantity of water and food. In most instances the Mosenthal<sup>1</sup> modification of the Hedinger and Schlayer<sup>2</sup> diet was administered. The urine was collected in two hour periods from 8 a. m. to 8 p. m., and in one period from 8 p. m. to 8 a. m.

Recently Mosenthal<sup>3</sup> and Schlayer and Beckmann<sup>4</sup> compared the effect of a low protein or bland diet with that of the usual test diet. The former author found that both had approximately the same effect on the urine. Schlayer and Beckmann observed that in severe cases of nephritis the bland diet gave results which were similar to those obtained with the usual diet; in less severe cases the variability of the volume and specific gravity was more marked in the case of the bland diet, while in mild cases the difference between the two diets was even more striking. Their bland diet was administered in five meals. It consisted of a cup of milk and a roll at breakfast, a cup of milk and a roll in the forenoon; a plate of unsalted cereal soup and 500 to 600 grams of porridge at noon; a cup of milk and a roll in the afternoon and 500 to 600 grams of porridge and a cup of milk for supper. In our series of bland dietary tests the patients received 840 c.c. of milk, 45 grams of bread, 12 grams of oatmeal and 50 grams of rice divided into five meals. The nitrogen content of the diet was about 6 grams, the sodium chlorid content about 1.6 grams and the calorie value 890.

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1. Mosenthal, H. O.: Arch. Int. Med., **16**:733, 1915.

2. Hedinger, M., and Schlayer: Deutsch. Arch. f. klin. Med. **114**:120, 1914.

3. Mosenthal, H. O.: Arch. Int. Med. **22**:770, 1918.

4. Schlayer and Beckmann: München. med. Wchnschr. **65**:92, 1918.

TABLE 1.—CASES SHOWING A MODERATE ABNORMALITY IN THE RENAL DIETARY TEST OR BLOOD ANALYSIS

Offi- cial Num- ber	Age	Diagnosis	Blood Pressure	Heart	Edema	Albu- min	Casts	Maximum Sp. Gr.	Vari- ation Sp. Gr.	Night Urine		Blood	
										Volume, C.c.	Sp. Gr.	Urea N, Mg., per Cent.	Uric Acid, Mg., per Cent.
5735	27	Chronic interstitial nephritis...	180-110	+	—	+	+	1.015	9	567	1.015	23.4	4.7
		Same case...	.....	+	—	—	—	1.020	4	515	1.019		
Obst.	17	Chronic interstitial nephritis...	192-120	—	—	—	—	1.009	4	750	1.009	19.6	3.1
3135	51	Chronic interstitial nephritis...	220-160	+	+	+	+	1.023	11	420	1.018	24.0	4.6
		Same case...	.....	+	+	+	+	1.023	6	666	1.017		
3069	19	Chronic interstitial nephritis...	125-83	+	+	+	+	1.020	0	900	1.020	17.4	
		Same case...	.....	+	+	+	+	1.020	5	750	1.018	16.0	2.1
4978	20	Chronic interstitial nephritis...	170	—	—	—	—	1.014	3	745	1.014	18.9	2.0
4398	28	Chronic interstitial nephritis...	140-90	+	—	—	—	1.030	9	124	1.030	31.0	4.1
4269	39	Chronic interstitial nephritis...	195-135	+	—	—	—	1.017	7	675	1.013	24.0	3.2
3484	24	Chronic interstitial nephritis...	120-80	+	—	—	—	1.022	19	400	1.020	25.0	6.6
3294	64	Chronic interstitial nephritis...	270-170	—	—	—	—	1.020	13	280	1.020	15.6	5.0
5885	27	Chronic interstitial nephritis...	200-128	—	—	—	—	1.010	4	230	1.008	15.0	1.8
		Same case...	.....	+	+	+	+	1.008	3	85	1.008		
5958	23	Chronic interstitial nephritis...	210-110	+	+	+	+	1.010	2	706	1.009	16.0	6.0
		Same case...	.....	—	—	—	—	1.010	2	1,160	1.009		
3222	19	Acute nephritis...	116-60	—	—	—	—	1.014	6	890	1.011	23.7	3.6
		Same case...	.....	+	—	—	—	1.016	9	780	1.011		
5037	20	Nephritis...	192-102	+	—	—	—	1.016	7	770	1.016	96.6	3.3
5640	19	Nephritis...	145-85	—	—	—	—	1.013	4	547	1.010	12.0	
		Same case...	.....	—	—	—	—	1.015	5	360	1.015		
4169	37	Syphilitic nephritis...	120-75	—	+	+	+	1.016	5	880	1.011	26.6	3.5
5384	50	Cardiorenal sclerosis...	182-112	+	—	—	—	1.020	8	415	1.023	26.0	
		Same case...	.....	+	—	—	—	1.019	4	510	1.019		
5794	45	Cardiorenal sclerosis...	225-120	+	—	—	—	1.015	2	100	1.013	13.0	3.2
		Same case...	.....	+	—	—	—	1.016	6	85	1.012		
4447	45	Cardiorenal sclerosis...	160-110	—	—	—	—	1.018	10	2,840	1.008	22.0	7.3
3078	69	Arteriosclerosis...	140-90	—	—	—	—	1.020	3	400	1.017	12.9	5.0
4725	64	Arteriosclerosis...	195-110	+	—	—	—	1.015	6	565	1.015	29.0	3.5
3633	51	Arteriosclerosis...	184-140	+	+	+	+	1.017	8	450	1.017	15.0	7.0
4436	62	Arteriosclerosis...	160-92	+	+	+	+	10.20	8	335	1.020	26.0	3.6
4029	50	Arteriosclerosis...	150-98	+	+	+	+	1.027	22	219	1.027	24.0	5.2
4511	60	Arteriosclerosis...	172	—	—	—	—	1.018	9	505	1.018	27.0	3.5
5055	28	Hysteria...	122-65	—	—	+	+	1.013	9	600	1.013	14.7	3.4

TABLE 2.—CASES SHOWING A SLIGHT ABNORMALITY IN THE RENAL DIETARY TEST OR BLOOD ANALYSIS

Clinical Number	Age	Diagnosis	Blood Pressure	Heart	Edema	Albumin	Casts	Maximum Sp. Gr.	Variation Sp. Gr.	Night Urine		Blood	
										Volume, C.c.	Sp. Gr.	Urea N, Mg. per Cent.	Uric Acid, Mg. per Cent.
3199	55	Chronic interstitial nephritis...	200-100	+	—	+	—	1.022	2	240	1.020	17.9	3.3
		Same case.....	.....	+	—	+	+	1.024	4	260	1.023	18.6	6.4
3301	21	Chronic interstitial nephritis...	148-48	+	—	+	+	1.033	18	250	1.033	13.5	5.1
		Same case.....	.....	+	—	+	+	1.023	16	276	1.022	13.5	5.1
		Same case.....	.....	+	—	+	+	1.027	24	228	1.027	23.4	2.4
5356	18	Same case.....	.....	+	—	+	+	1.021	11	575	1.013	23.4	2.4
4254	44	Chronic interstitial nephritis...	190-110	—	—	—	—	1.020	12	725	1.014	28.0	2.8
Ped.	10	Chronic interstitial nephritis...	140-80	—	—	—	—	1.022	9	109	1.022	22.4	1.0
4682	33	Chronic interstitial nephritis...	108-86	+	—	+	+	1.025	16	197	1.025	18.0	4.0
3666	23	Chronic interstitial nephritis...	140-80	+	—	+	+	1.022	15	365	1.022	18.0	4.0
3569	22	Chronic interstitial nephritis...	130-64	—	—	—	—	1.020	15	370	1.014	10.0	3.2
		Chronic interstitial nephritis...	150-90	—	—	—	—	1.020	8	530	1.020	6.7	3.3
		Same case.....	.....	—	—	—	—	1.019	17	400	1.018	18.6	4.2
3856	29	Chronic interstitial nephritis...	140-90	—	—	—	—	1.020	13	1,000	1.007	14.4	1.5
3451	56	Chronic interstitial nephritis...	194-126	—	—	—	—	1.030	7	380	1.026	19.0	4.0
3309	32	Chronic interstitial nephritis...	158-90	—	—	—	—	1.021	9	700	1.012	16.3	2.7
3290	50	Chronic interstitial nephritis...	220-110	+	—	+	+	1.020	4	555	1.017	21.0	3.4
		Same case.....	.....	+	—	+	+	1.020	4	365	1.018	16.5	1.6
4952	38	Chronic interstitial nephritis...	240-140	+	—	+	+	1.013	10	885	1.013	16.1	3.7
4951	40	Chronic interstitial nephritis...	172-105	+	—	+	+	1.023	13	280	1.021	13.2	2.7
5834	33	Chronic interstitial nephritis...	144-88	+	—	+	+	1.027	4	275	1.026	13.2	2.7
		Same case.....	.....	—	—	—	—	1.021	8	205	1.019	14.6	4.5
5984	44	Chronic interstitial nephritis...	135-87	—	—	—	—	1.016	8	405	1.016	23.1	2.4
		Same case.....	.....	+	—	+	+	1.017	3	390	1.017	19.0	2.7
5971	66	Chronic interstitial nephritis...	198-120	+	—	+	+	1.016	8	440	1.010	23.1	2.4
		Same case.....	.....	—	—	—	—	1.022	14	303	1.022	19.0	2.7
4190	18	Chr. parenchymatous nephritis...	145-100	—	—	—	—	1.027	13	303	1.022	23.1	2.4
5030	24	Chr. parenchymatous nephritis...	130-78	+	—	+	+	1.025	14	455	1.012	19.0	2.7

3166	29	Acute parenchymatous nephritis	155-90	-	+	..	..	1.016	11	170	1.015	13.7	2.5
4215	22	Same case.....	122-84	..	+	..	+	1.018	4	190	1.018	19.1	4.5
Ped.	3	Acute nephritis.....	.....	..	+	..	+	1.025	18	262	1.025	22.4	3.0
3683	58	Same case.....	.....	..	+	..	+	1.024	11	91	1.022	14.2	3.8
		Chronic interstitial nephritis...	127-87	..	+	..	+	1.014	7	250	1.014		
		Same case.....	.....	..	+	..	+	1.018	11	335	1.018		
3144	45	Cardiorenal sclerosis.....	135-85	..	+	..	+	1.019	11	562	1.013	14.0	2.9
4129	55	Cardiorenal sclerosis.....	100-90	..	+	..	+	1.024	9	225	1.024	15.4	4.7
4372	45	Cardiorenal sclerosis.....	180-90	..	+	..	+	1.027	18	218	1.027	23.0	2.4
3113	61	Arteriosclerosis.....	159-90	..	+	..	+	1.018	15	544	1.018	16.8	2.0
		Same case.....	.....	..	+	..	+	1.018	17	370	1.017		
3545	52	Arteriosclerosis.....	218-123	..	+	..	+	1.018	8	380	1.018	11.7	4.2
		Same case.....	.....	..	+	..	+	1.022	7	230	1.020	18.2	4.0
3017	50	Arteriosclerosis.....	248-170	..	+	..	+	1.030	10	200	1.030	16.8	3.0
4142	52	Arteriosclerosis.....	130-60	..	+	..	+	1.031	20	230	1.028	16.0	5.0
4234	38	Arteriosclerosis.....	150-80	..	+	..	+	1.027	9	220	1.027	12.0	3.8
4507	57	Arteriosclerosis.....	108-98	..	+	..	+	1.020	14	250	1.020	23.0	2.0
4220	66	Arteriosclerosis.....	144-80	..	+	..	+	1.022	15	320	1.022	26.0	3.2
3350	52	Arteriosclerosis.....	210-110	..	+	..	+	1.023	8	250	1.019	18.0	3.4
4070	55	Arteriosclerosis.....	200-120	..	+	..	+	1.021	8	325	1.020	18.6	3.2
4094	58	Arteriosclerosis.....	215-155	..	+	..	+	1.025	4	380	1.025	23.8	1.4
3120	59	Arteriosclerosis.....	240-100	..	+	..	+	1.018	6	387	1.018	11.4	3.5
3027	18	Renal tuberculosis.....	120	..	+	..	+	1.027	19	940	1.010	14.0	1.7
		Same case.....	135-87	..	+	..	+	1.023	7	340	1.019	17.7	5.2
4944	25	Hematuria.....	125-55	..	+	..	+	1.023	5	240	1.021	30.8	3.1
5578	50	Cardiac decompensation.....	.....	..	+	..	+	1.020	11	345	1.020	16.2	
		Same case.....	.....	..	+	..	+	1.023	8	280	1.025		
4973	15	Endocarditis.....	115-70	..	+	..	+	1.034	19	1,110	1.008	17.5	3.1
4171	23	Trichiniasis.....	110-78	..	+	..	+	1.027	24	450	1.007	11.2	1.0
4985	24	Facial paralysis.....	180-110	..	+	..	+	1.020	15	265	1.020	26.8	3.2
5739	19	Peliosis rheumatica.....	126-68	..	+	..	+	1.015	6	475	1.015	14.0	
		Same case.....	.....	..	+	..	+	1.024	12	515	1.023		
5866	47	Arthritis deformans.....	120-72	..	+	..	+	1.024	12	330	1.012	12.3	5.1
		Same case.....	.....	..	+	..	+	1.026	11	155	1.026		
3399	27	Hysteria.....	128-80	..	+	..	+	1.026	8	275	1.026	21.0	1.0
4980	19	Peripheral neuritis...	110-76	..	+	..	+	1.027	20	385	1.023	26.0	
Oph.	29	Iridocyclitis.....	128	..	+	..	+	1.036	6	290	1.021	15.1	3.8

TABLE 3.—CASES SHOWING NO ABNORMALITY IN THE RENAL DIETARY TEST OR BLOOD ANALYSIS

Clinical Number	Age	Diagnosis	Blood Pressure	Heart	Edema	Albumin	Casts	Maximum Sp. Gr.	Variation Sp. Gr.	Night Urine		Blood	
										Volume, C.c.	Sp. Gr.	Urea N, Mg. per Cent.	Uric Acid, Mg. per Cent.
3908	27	Chronic interstitial nephritis...	160-95	—	—	—	+	1.022	14	270	1.018	18.0	1.7
3301	45	Chronic interstitial nephritis...	210-110	+	—	+	—	1.023	13	325	1.025	13.0	1.0
3689	27	Chronic interstitial nephritis...	122-78	—	—	+	+	1.028	16	350	1.028	15.0	2.5
3071	38	Chronic interstitial nephritis...	180-120	—	—	+	—	1.022	9	325	1.020	17.0	1.8
3087	37	Chronic interstitial nephritis...	130-85	—	—	+	—	1.019	17	325	1.019	16.0	1.8
5583	48	Chronic interstitial nephritis...	120-70	+	—	+	+	1.019	13	407	1.019	16.0	1.4
6095	32	Chronic interstitial nephritis...	140-90	+	—	+	+	1.027	10	170	1.027	14.2	1.8
		Same case.....	.....	.....	.....	.....	.....	1.033	10	300	1.033		
6016	45	Chronic interstitial nephritis...	104-78	—	—	—	+	1.033	10	300	1.033	22.0	1.9
		Same case.....	.....	.....	.....	.....	.....	1.033	10	190	1.033	11.6	1.9
6077	43	Chronic interstitial nephritis...	198-110	+	+	+	+	1.024	12	245	1.024	17.4	1.9
6105	26	Chronic interstitial nephritis...	150-100	+	—	+	+	1.035	24	300	1.021		
		Same case.....	.....	.....	.....	.....	.....	1.031	19	140	1.031	15.4	1.6
6145	47	Chronic interstitial nephritis...	170-110	+	+	+	+	1.021	15	215	1.021	16.4	2.1
6091	51	Chronic interstitial nephritis...	140-78	—	—	+	—	1.021	20	190	1.021		
		Same case.....	.....	.....	.....	.....	.....	1.024	15	205	1.024	14.0	1.2
3339	25	Acute nephritis.....	140-60	+	+	+	+	1.019	12	325	1.016	18.0	2.6
5736	18	Albuminuria.....	120-75	—	—	+	+	1.025	16	320	1.016	7.7	
5050	24	Nephrosis.....	120-88	—	+	+	+	1.029	9	220	1.020		
		Same case.....	.....	.....	.....	.....	.....	1.029	9	265	1.021	21.0	1.0
4209	49	Arteriosclerosis.....	210-110	—	—	—	+	1.027	20	345	1.021	8.0	
3035	57	Arteriosclerosis.....	175-95	—	—	—	—	1.030	20	220	1.020		2.5

4049	32	Pregnancy.....	128- 68	-	-	-	-	-	1.024	10	330	1.024	25.0	1.0
Gyn.	23	Pregnancy.....	110- 60	-	-	-	-	-	1.020	12	300	1.020	18.0	1.0
Gyn.	30	Pregnancy.....	120- 60	-	-	-	-	-	1.023	17	170	1.023	16.0	1.0
5995	14	Congenital syphilis.....	120- 68	-	-	-	-	-	1.021	13	190	1.021		
		Same case.....		-	-	-	-	-	1.026	20	250	1.026		
6021	45	Cerebrospinal syphilis.....	100- 50	-	-	-	-	-	1.020	14	160	1.020		
		Same case.....		-	-	-	-	-	1.025	20	290	1.025		
6048	28	Neurasthenia.....	130- 60	-	-	-	-	-	1.024	18	130	1.024	11.4	1.8
		Same case.....		-	-	-	-	-	1.032	10	140	1.032		
5990	24	Neurasthenia.....	135- 68	-	-	-	-	-	1.028	20	202	1.028	11.4	1.4
		Same case.....		-	-	-	-	-	1.035	31	250	1.035		
5495	18	Neurasthenia.....	118- 50	-	-	-	-	-	1.030	15	252	1.025	16.0	1.5
6042	30	Neurasthenia.....	115- 58	-	-	-	-	-	1.025	18	160	1.025		
		Same case.....		-	-	-	-	-	1.026	22	195	1.026		
4990	21	Primary optic atrophy.....	120- 80	-	-	-	-	-	1.029	18	360	1.025	16.0	2.0
5937	15	Chorea.....		-	-	-	-	-	1.031	16	155	1.031		
		Same case.....		-	-	-	-	-	1.029	23	210	1.029		
5789	42	Morphinism.....	135- 90	-	-	-	-	-	1.021	17	245	1.021	16.0	1.5
		Same case.....		-	-	-	-	-	1.029	15	232	1.022		
5808	52	Acronegaly.....	120- 70	-	-	-	-	-	1.029	12	348	1.020	18.0	1.3
		Same case.....		-	-	-	-	-	1.035	13	222	1.030		
6036	16	Polyglandular insufficiency.....	110- 65	-	-	-	-	-	1.023	15	312	1.023		
		Same case.....		-	-	-	-	-	1.023	17	280	1.023		
Surg.	15	Hyperthyroidism.....	135	-	-	-	-	-	1.036	14	98	1.036	13.2	1.4
		Same case.....		-	-	-	-	-	1.029	19	120	1.029		
6072	26	Gonorrheal rheumatism.....	112- 70	-	-	-	-	-	1.028	11	280	1.028	15.4	1.9
6151	31	Hysteria.....	128- 72	-	-	-	-	-	1.024	10	155	1.024		
		Same case.....		-	-	-	-	-	1.028	19	180	1.028		
6050	18	Bronchopneumonia.....		-	-	-	-	-	1.020	12	400	1.020		
		Same case.....		-	-	-	-	-	1.025	19	350	1.019		

## DISCUSSION

Depending in a general way on the degree of abnormality, the cases have been tabulated in three groups. The cases showing marked abnormality have been omitted. In addition to the laboratory findings, the clinical number, age, diagnosis, systolic and diastolic blood pressures, presence of cardiac enlargement, edema, albumin and casts have been considered. The following norms have been adopted for the dietary tests and blood analyses: Maximum specific gravity, eighteen or higher; variation in specific gravity nine or more; volume of the night urine 400 c.c. or less; specific gravity of the night urine eighteen or more; urea nitrogen concentration of the blood 0.020 grams per cent. or less, and the uric acid concentration of the blood 0.0025 grams per cent. or less.

Tables 1 and 2 summarize the data of 100 cases showing moderate and slight abnormality, respectively. All showed renal involvement from the clinical point of view. *Sixty-six per cent. had an abnormality in the dietary test, while 74 per cent. showed an increased concentration of uric acid in the blood.* Myers and collaborators<sup>5</sup> have pointed out that in nephritis the uric acid content of the blood is increased long before urea. Mosenthal and Lewis<sup>6</sup> compared the delicacy of the various tests for renal function, but omitted consideration of the blood uric acid. They concluded that the dietary test was the most delicate.

It follows from the above that the uric acid concentration of the blood is a delicate, if not the most delicate, index of renal function at our disposal. The individual abnormalities in our series were as follows: Twenty-six as regards maximal specific gravity, forty-nine as regards variability of specific gravity, forty as regards volume or concentration of the night urine and thirty-five as regards urea nitrogen content of the blood. An abnormal dietary test with normal blood findings was found in 8 per cent. of the cases. An abnormally high urea with a normal uric acid concentration was encountered in only six instances. The figures in Tables 1 and 2, but particularly those in Table 3 indicate\* that 400 c.c. is the upper normal limit for the volume of the night urine, provided the patients are kept in bed during the test period. At any rate we have never found more in an individual in whom there was no reason to suspect renal involvement.

If each test is considered as a whole, the figures of Table 4 indicate that the results are similar with either the bland or the relatively

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5. Myers, V. C., and Fine, M. S.: J. Biol. Chem. **20**:391, 1915. Myers, V. C.; Fine, M. S., and Lough, W. G.: Arch. Int. Med. **17**:570, 1916. Chace, A. F., and Myers, V. C.: J. A. M. A. **67**:929, 1916.

6. Mosenthal, H. O., and Lewis, D. S.: J. A. M. A. **67**:933, 1916.

high protein and salt diets. Owing to the small quantity of solids which it contains, the bland diet tends to lower the specific gravity of the night urine. As one would expect in cases with fixation of specific gravity the volume of the night urine is greater on the regular than on the bland diet. On the whole, it appears that both tests may be used interchangeably. The advantages of the bland diet are that it is easily prepared, and that it may be used where a high protein diet is undesirable or where digestive disturbances are present.

TABLE 4.—COMPARISON OF THE DATA OF BOTH DIETARY TESTS, BLAND AND REGULAR

Maximum Sp. Gr.		Variation Sp. Gr.		Total Volume, C.c.		Night Urine			
						Volume, C.c.		Sp. Gr.	
Bland	Regu- lar	Bland	Regu- lar	Bland	Regu- lar	Bland	Regu- lar	Bland	Regu- lar
1.010	1.010	2	2	1,764	2,783	760	1,160	1.009	1.009
1.021	1.026	10	17	1,070	1,066	290	310	1.021	1.025
1.022	1.020	16	16	1,128	1,754	395	304	1.015	1.020
1.020	1.020	16	14	1,305	1,185	260	350	1.020	1.020
1.026	1.019	3	4	833	1,194	415	510	1.023	1.019
1.015	1.013	5	4	1,163	1,340	360	567	1.015	1.010
1.017	1.021	6	3	1,593	1,127	615	590	1.017	1.021
1.029	1.035	12	13	744	492	348	222	1.020	1.030
1.015	1.016	2	8	593	944	100	85	1.013	1.012
1.023	1.036	22	31	1,013	600	257	165	1.009	1.029
1.015	1.024	6	12	1,694	1,436	457	515	1.015	1.023
1.015	1.020	9	4	1,807	1,177	567	515	1.015	1.019
1.021	1.029	17	15	1,287	561	245	232	1.021	1.022
1.010	1.008	4	3	762	671	230	85	1.008	1.008
1.022	1.019	16	10	1,016	1,062	380	310	1.016	1.017
1.023	1.027	13	3	808	676	280	275	1.021	1.026
1.025	1.030	16	10	1,213	641	320	232	1.016	1.030
1.009	1.010	0	1	1,506	1,705	845	935	1.009	1.009
1.025	1.024	17	7	1,899	1,343	370	490	1.025	1.024
1.024	1.026	18	11	965	590	330	155	1.012	1.026
1.033	1.033	9	9	678	833	300	150	1.033	1.033
1.021	1.016	8	7	823	1,600	205	405	1.019	1.016
1.029	1.022	9	12	370	757	220	510	1.020	1.010
1.016	1.017	8	3	1,300	670	440	360	1.010	1.017
1.028	1.035	20	31	1,157	1,570	202	220	1.028	1.035
1.014	1.018	7	12	1,595	1,652	250	335	1.014	1.018
1.028	1.027	24	17	979	963	305	312	1.016	1.026
1.024	1.032	18	10	1,405	520	130	140	1.024	1.032
1.027	1.033	10	12	447	507	170	200	1.027	1.033
1.021	1.026	13	20	1,638	2,315	190	250	1.021	1.026
1.031	1.029	16	23	674	1,377	155	210	1.031	1.029
1.025	1.026	18	22	1,315	1,750	160	195	1.025	1.026
1.020	1.025	14	20	1,460	2,680	160	290	1.020	1.025
1.028	1.026	11	16	760	1,120	280	280	1.028	1.026
1.035	1.031	24	19	953	836	300	140	1.021	1.031
1.023	1.023	15	17	1,467	2,180	312	280	1.023	1.023
1.020	1.025	13	19	1,700	1,575	400	350	1.020	1.019
1.036	1.029	14	19	224	725	98	120	1.036	1.029
1.022	1.034	17	24	1,690	1,262	700	950	1.014	1.010
1.024	1.028	10	19	590	657	155	180	1.024	1.028

#### CONCLUSIONS

In conclusion, we wish to emphasize the desirability of keeping the patients in bed during the test period. Even then the results may be unreliable in the presence of edema, cardiac decompensation or when the urine is scanty or highly concentrated as in midsummer. Needless to say all forms of treatment must be interdicted during the test period.

# ON THE CLINICAL EVIDENCE OF INVOLVEMENT OF THE SUPRARENAL GLANDS IN INFLU- ENZA AND INFLUENZAL PNEUMONIA \*

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During the recent epidemic of influenza and influenzal pneumonia, we were impressed with the marked degree of asthenia present in all cases. No matter how mild the attack, asthenia was almost invariably one of the most, if not the most, prominent symptom. It was usually out of all proportion to the other symptoms and persisted not only during the attack but far into convalescence. When we review the summaries of chief complaints recorded in the literature, we find that this was the general observation. Certain symptoms were more common in some localities than in others, but asthenia was the symptom common to the disease in all localities.

In our series of cases<sup>1</sup> we were unable to satisfy ourselves with the prevailing belief that the prostration was due to cardiovascular disease. Our attention was called to the possible existence of disturbed function of the suprarenal glands early in the epidemic, whereupon we instituted epinephrin treatment in a series of cases.

The most common and the most marked symptom of suprarenal insufficiency is asthenia (prostration). Low blood pressure, another cardinal symptom of suprarenal insufficiency, has been commonly observed by clinicians as characteristic of influenza and influenzal pneumonia. We became interested in determining, on purely clinical grounds, if possible, whether a hypoadremia or a disturbance of the chromaffin system could be shown to be at the bottom of the symptom group so much in the foreground in this disease.

The French school, among whom should be mentioned Josue,<sup>2</sup> Netter,<sup>3</sup> Sergent,<sup>4</sup> Renon<sup>5</sup> and Florand,<sup>6</sup> has emphasized its belief that

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\* From the Department of Pediatrics and Contagious Diseases, University of Michigan.

\* Read at the Meeting of the American Society for Clinical Investigation, Atlantic City, June 14, 1919.

1. Cowie, D. M., and Beaven, P. W., Jr.: *J. Michigan M. S.* **18**:42 (Feb.) 1919.

2. Josué: *Bull. et mem. Soc. med. d. hôp. de Par.* 904 (Oct. 11) 1918.

3. Netter, A.: *Ibid.* p. 903.

4. Sergent, E.: *Ibid.* p. 905.

5. Rénon, L.: *Ibid.* p. 905, quoted by Sergent.

6. Florand, A.: *Ibid.* p. 905, quoted by Sergent.

suprarenal pathology is present in influenza and is responsible for the symptom of asthenia. In this country Kelman and Calhoun<sup>7</sup> found evidence of suprarenal dysfunction in a series of over twenty necropsies.

*Demonstration of Suprarenal Insufficiency in Many of the Acute Infections.*—In 1900, Evans<sup>8</sup> reported a case of typhoid fever in which during convalescence symptoms of suprarenal insufficiency began to develop—marked asthenia, low blood pressure, bronze skin and diarrhea. Evans asks whether suprarenal insufficiency is a complication of a primary condition, typhoid in this instance. Lavenson<sup>9</sup> has shown that from an adjacent suppurative process in the lungs thrombosis of the suprarenal veins may occur and bring about a necrosis of the suprarenals. Dock<sup>10</sup> remarks that lung conditions, such as pneumonia, favor inflammation and softening of the suprarenals.

Probably the most striking illustrations of pneumonias so complicated are to be found in the cases reported by Murray,<sup>11</sup> Greenhow<sup>12</sup> and Sicard.<sup>13</sup> Murray's case was a severe pneumonia which presented, in addition to the pneumonic symptoms, remarkable prostration and a general duskiness of the skin. The mucous membranes were not involved. This patient died, apparently from exhaustion. Necropsy showed an extravasation of blood into both suprarenal capsules. The center of the right capsule was plugged with a firm black clot. Greenhow's case was a pneumonia, the chief symptom of which was weakness, which continued throughout the disease until death. In this case the right suprarenal was found to be enlarged, firm and fibrous; the left suprarenal was converted into a sac filled with a coagulum. Sicard's case was a bacillus Friedländer's pneumonia, the chief symptom of which was also asthenia. The asthenia was so marked that the patient presented signs difficult to differentiate from those of bulbo-spinal myasthenia. Necropsy showed hemorrhage into the center of both suprarenals.

The opinion is fixed so firmly that the suprarenals are involved in many of the acute infections that the French school, fathered by Sergent,<sup>14</sup> assumes its presence, and claims one is justified in making a diagnosis of suprarenal insufficiency whenever the characteristic

7. Kelman, S., and Calhoun, H.: Personal communication.

8. Evans, H. W.: *Lancet* **1**:1655 (June 9) 1900.

9. Lavenson, R. S.: *Arch. Int. Med.* **2**:68 (Oct.) 1908.

10. Dock, G.: *Osler's Syst. Med.* **4**:783.

11. Murray, J.: *Trans. Path. Soc., Lond.* **21**:395, 1870.

12. Greenhow, E. H.: *Tr. Path. Soc. Lond.* **28**:231, 1877.

13. Sicard, M.: *Soc. med. d. hôp. d. Par.*, p. 848, 1904.

14. Sergent: *Arch. gen. de med.* **193**:17, 1904.

symptoms can be demonstrated. Sergent<sup>15</sup> believes that this complication follows certain infections as regularly as nephritis follows scarlet fever, and in precisely the same manner. Chief among the supporters of this idea is Bossuet.<sup>16</sup> Indeed, few of the French clinicians dissent from Sergent's view.

*Pathologic Evidence That the Suprarenals Are Affected in Influenzal Pneumonia.*—While this is purely a clinical and not a pathologic study, it is, nevertheless, of paramount interest to know whether necropsies performed in cases of influenzal pneumonia throw any light on the question. The findings of Kelman and Calhoun,<sup>7</sup> to which we have already referred, are significant. Through the courtesy of the department of pathology, we have reports of the suprarenal findings in eleven cases of influenzal pneumonia. It is unfortunate that we cannot present more cases. These were all necropsies permitted by the military authorities on over seventy patients belonging to the S. A. T. C. who died of the disease.

In these necropsies, six cases showed hypoplasia, and one case a moderate atrophy, but in no cases did hemorrhage into or necrosis of the suprarenals occur. The hypoplasia, however, was associated with a "status lymphaticus" in all but one case.

We must admit that from the records of the pathologic department we have not a clear case of suprarenal disease, but surely one which raises the question: Does hypoplasia of the gland signify its hypofunction? In this particular group of cases, we think no other question can arise. It may not be out of place, at this point, to call attention to the fact, so frequently demonstrated, that an organ may fail to functionate almost, if not completely, so far as certain of its secretions are concerned and yet give no evidence of anatomic change (the gastric mucosa in pernicious anemia and achylia gastrica).

*Symptoms of Suprarenal Insufficiency.*—The chief symptoms of suprarenal insufficiency are asthenia, prostration and lowered blood pressure. These are alike common to acute or chronic suprarenal insufficiency. In our series of influenza and influenzal pneumonia cases, these findings were invariably present, but there were other symptoms common to the disease which are characteristic of acute suprarenal insufficiency not of influenzal origin, such as nausea, vomiting, abdominal pain (epigastric and appendiceal), pains in the back and even tenderness on pressure over the back muscles, and in a few cases diarrhea. Lavenson has attempted a grouping of various symptoms presented by the cases of known suprarenal insufficiency which have

15. Sergent, E.: J. de med., 753 (Oct. 10) 1917.

16. Bossuet, G.: Gaz. hebdomadaire de médecine et de chirurgie, 25:524, 1904, quoted by Lavenson (9).

been recorded, and he describes (1) what may be called the abdominal type in which sudden death was preceded by marked abdominal symptoms; (2) the asthenic type; (3) the nervous type characterized by convulsions, and (4) cases of sudden death in which at necropsy no pathology except that present in the suprarenals could be found. In influenza and influenzal pneumonia it is not difficult to differentiate cases suitable to the first three groupings. We will discuss other, possibly more definite, signs of suprarenal insufficiency in the following paragraphs.

*Tests for Suprarenal Insufficiency.*—Blood Pressure: We took pressures on a group of unselected cases with no regard to the stage of the disease. Five were cases complicated with pneumonia and twenty were uncomplicated influenzas. The average systolic pressure of the pneumonias was 99. The average systolic pressure of the influenzas was 115. This is a lowered pressure when one takes into consideration the fact that the patients ranged in age from 20 to 40. In one case of influenza the blood pressure was 105. The patient, a medical student, stated that he had had his blood pressure taken previous to the disease and it had registered 130 systolic. Keeton and Cushman report that in a series of fifty-seven observations 42 per cent. of the patients had systolic pressures of 110 or below. Josue<sup>2</sup> states that in almost every case of influenza that came under his observation the patient had a low blood pressure even if pneumonia did not complicate the case.

Low blood pressure is the rule in suprarenal insufficiency whether it is caused by tuberculosis, syphilis, cirrhosis or hemorrhage into the suprarenals, and whether it is acute or chronic. Dock<sup>10</sup> records four cases of Addison's disease in which the pressures were 110, 108, 85 and 83. In two other cases taken from his records in this hospital,<sup>17</sup> we find the systolic pressure in one case varying between 85 and 110, in the other between 84 and 107. In the case we record in Table 1, the systolic pressure varied between 84 and 100. Higher blood pressures have been recorded in Addison's disease. Janeway has reported a case in which the systolic pressure was 140. This, however, is a very rare finding. Gruenbaum,<sup>18</sup> in a synopsis of his cases of Addison's disease, concludes that the systolic pressure averages about 100. Schaffner and Howard<sup>19</sup> report one of the few cases of syphilitic involvement of the suprarenal gland. In this case the systolic pressure was 98. In Sergeant's<sup>14</sup> case of fibrosis of the suprarenals there was a marked arterial hypotension. In Sicard's<sup>13</sup> case of acute suprarenal

17. Numbers 08-623 and 05-38.

18. Gruenbaum, O.: Practitioner, Lond. **79**:218 (Aug.) 1907.

19. Schaffner, P. M., and Howard, T.: New York M. J. 1026, (May 27) 1916.

insufficiency, where necropsy revealed hemorrhage into the gland, the systolic pressure was 78 (or 7.8 Potain's sphygmomanometer). It is not unreasonable to conclude that the blood pressure observed in influenza and especially in the complicating pneumonia, corresponds to what we should expect to find.

We must consider the fact that low blood pressures are commonly found in certain other diseases not of influenzal origin, for example, diphtheria<sup>20</sup> and croupous pneumonia. These diseases present this finding when the myocardium is weakened, and at such a time, unquestionably, this defect plays a rôle in bringing about the reduced pressure. It is known that diphtheria toxin in the circulation calls forth all the available epinephrin to combine with it and render it harmless.<sup>21</sup> That epinephrin antagonizes diphtheria toxin has been shown by injecting it at the time of, or shortly after, injecting a fatal dose of diphtheria toxin, in which case the animal survives.<sup>21</sup>

One can conceive of the demand for epinephrin by the toxin being so great as to exhaust the suprarenals and other chromaffin tissues, and thus cut off one of the potent factors in sustaining normal blood pressure. We have previously cited instances of pneumonia in which the suprarenals were involved. We are not sure that this is not a common occurrence and that it may be responsible for the lowered pressure in this disease. It is not at all improbable that the pathologist's zeal to seek for signs of dysfunction in this organ has been no less marked than that of the clinician's to interpret the significance of what have been determined to be quite well-marked manifestations of adrenal insufficiency.

In our series of cases referred to before,<sup>1</sup> we were unable to demonstrate evidence of significant weakened heart action. To us it seems credible to regard the lowered blood pressure in influenza and influenzal pneumonia as due to causes other than those of myocardial origin. It may be endocrinal.

*Rise of Systolic Pressure After Prolonged Administration of Epinephrin.*—After giving suprarenal extract in 3-grain doses, three times daily, in cases of suprarenal deficiency, Gruenbaum<sup>18</sup> reports a rise of 10 mm. Hg at the end of the third day, which did not occur in the control cases. Of five influenzal patients, whom we selected to test out this point, one was in the acute stage of the disease, and subsequent observation showed that he was developing pneumonia at the time of the test. This patient had a systolic pressure of 119 before the epinephrin was given. He was given 10 minims of epinephrin<sup>22</sup>

20. A case in our clinic showed a systolic pressure of 84.

21. Marie, A.: Ann. de l'Inst. Pasteur, March, 1918.

22. Fresh adrenalin (Parke, Davis & Co.), 1:1,000 solution, was used in all experiments.

intramuscularly, four times daily, for three days. At the end of this time his pressure was taken with the precaution that five hours had elapsed since the last injection. It was found to be 131. In the other four cases, treated in the same way, with the patients convalescent at the time of the test, no effect on the blood pressure was observed. In the control cases (patients in hospital for other reasons) no rise in pressure was noted. If this test is as valuable as Gruenbaum regards it, we may assume a suprarenal insufficiency in the first case cited, an acute case.

*Maintenance of Pressure with Epinephrin.*—Two years ago Beaven studied a case of Addison's disease in the medical clinic (No. 17-546) in which the diagnosis was confirmed by necropsy. He made the following observations: If 1 c.c. of epinephrin was injected intramuscularly, after the initial rise, the systolic pressure would remain elevated longer than it would in a normal individual. The result of this case together with that of a series of influenza and normal cases is given in Table 1.

TABLE 1.—THE EFFECT OF EPINEPHRIN ON THE BLOOD PRESSURE CURVE

Case Number	Name	Diagnosis	Control Pressure	Systolic Blood Pressure after Subcutaneous Injection of 1 Mg. Epinephrin					
				1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	7 Hours
1	....	Addison's	84	112	...	93			
2	C. F.	Pneumonia	103	118	126	113	...	108	103
3	J. N.	Pneumonia	90	142	99	90	...	91	
4	W. T.	Influenza	128	140	148	135	...	128	
5	E. M.	Influenza	106	...	120	...	110	105	
6	C. S.	Influenza	105	...	128	...	118	104	
7	A. L.	Influenza	106	...	126	115	106	105	
8	A. R.	Mumps	130	135	128	125	...	132	
9	P. B.	Normal	120	126	118	115	...	120	
10	C. H.	Normal	112	118	106	106	...	110	

This table shows that the cases of influenza and influenzal pneumonia simulate the result obtained in Addison's disease. The normal cases reached their height a few minutes after the injection, and at the end of an hour the pressure had returned, practically, to normal. At the end of two hours, the pressure was normal in both cases. The mumps case also follows the normal curve. The analogy presented by this investigation may be significant.

*The Leukocytic Picture.*—We have shown, and so have others,<sup>1, 23</sup> that a low leukocyte count and a tendency to a leukopenia is the rule in influenza and influenzal pneumonia of the adult type. When we take from a series of ninety cases all those patients who lived, on the one hand, and all those who died, on the other, we obtain the following

23. Keeton, R. W., and Cushman, A. B.: J. A. M. A. **71**:1964, 1918.

averages in the leukocyte counts. Those that lived had a white count of 8,300 made up of polymorphonuclears, 75 per cent. and lymphocytes, 25 per cent. Those who died had a white count of 6,500, of which 61 per cent. were polymorphonuclears and 39 per cent. were lymphocytes. We observe that there is practically a normal leukocyte count, and that the differential count is not changed markedly. This is the same blood picture one finds in Addison's disease.<sup>10</sup> and it is interesting to note that the same low count and tendency to a leukopenia is present in typhoid fever, a disease which is also characterized by low blood pressure.<sup>24</sup>

*Tests for Endocrinal Dysfunction Applied to Influenza and Influenzal Pneumonia.*—A. Blood Sugar: One of the frequent findings in disturbances of endocrinal origin is a hypoglycemia.<sup>25</sup> We have made blood sugar determinations in a series of thirteen influenza cases and eight influenzal pneumonia cases with this point in view. None of the cases recorded had received any epinephrin during the course of their illness. The estimations were made at various stages of the disease, and the blood samples were taken at least three hours after the ingestion of food. The determinations were made by the Lewis and Benedict method, and are recorded in Table 2. It will be seen that the blood sugar was always within normal limits. There does not seem to be any relation between the period of the disease, the amount of prostration and the glycemia. We call attention to this latter point in particular, because McCrudden and Sargent<sup>26</sup> explain the myasthenia of progressive muscular dystrophy on the basis of hypoglycemia. On the other hand, one cannot assume that a hypoglycemia is pathognomonic of endocrinal disturbance, since it is not always found, and since in certain endocrinal diseases a hyperglycemia is frequently found (exophthalmic goiter).

B. Blood Sugar Changes Following the Intramuscular Injection of 1 mg. of Epinephrin: The occurrence of a temporary rise in the normal blood sugar curve after the injection of epinephrin is well known. Not finding a hypoglycemia, we attempted to demonstrate a difference in the excretion curve after an artificial hyperglycemia induced by the epinephrin injection. Hamman and Hirschman<sup>27</sup> have shown that after the injection of one milligram of epinephrin in a diabetic (Cases 12 and 24) in place of the normal "prompt rise in the blood sugar

24. Carter, H. S.; Orr, and Norris, G. W.: Quoted by Morris and Edmunds, *Med. News*, Jan. 14, 1905.

25. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: *Arch. Int. Med.* **21**: 188 (Feb.) 1918.

26. McCrudden, R. H., and Sargent, C. S.: *Arch. Int. Med.* **17**:471 (April) 1916.

27. Hamman, L., and Hirschman, I. I.: *Arch. Int. Med.* **20**:762 (Dec.) 1917.

which reached its maximum in a half to one hour, and then rapidly subsided, the whole reaction being over in two hours," there is a prolonged blood sugar curve characterized by a slow rise which may or may not be high, but is well sustained, and may not return to normal until beyond two and a half hours after the injection. We have applied this test to a series of influenza and influenzal pneumonia and control

TABLE 2.—BLOOD SUGAR DETERMINATIONS IN INFLUENZA AND INFLUENZAL PNEUMONIA

Case Number	Name	Diagnosis	Day of Disease	Degree of Prostration	Blood Sugar Reading
1	M. L.	Influenza	1	Acute	0.103
2	R. McC.	Influenza	2	Moderate	0.116
3	W. R.	Influenza	2	Acute	0.097
4	T. J.	Influenza	2	Moderate	0.104
5	D. S.	Influenza	2	Moderate	0.088
6	M. L.	Influenza	3	Mild	0.081
7	M. L.	Influenza	3	Mild	0.122
8	C. S.	Influenza	3	Acute	0.097
9	E. M.	Influenza	4	Acute	0.105
10	M. S.	Influenza	5	Mild	0.106
11	A. S.	Influenza	5	Mild	0.118
12	W. McK.	Influenza	7	Mild	0.142
13	E. M.	Influenza	10	Mild	0.104
14	L. T.	Pneumonia	1	Acute	0.132
15	P. M.	Pneumonia	2	Acute	0.120
16	C. F.	Pneumonia	3	Moderate	0.103
17	F. R.	Pneumonia	3	Acute	0.096
18	M. L.	Pneumonia	5	Acute	0.134
19	M. R.	Pneumonia	8	Acute	0.104
20	F. M.	Pneumonia	15	Acute	0.166
21	F. B.	Pneumonia	24	Moderate	0.107

TABLE 3.—THE EFFECT OF INJECTION OF 1 MG. EPINEPHRIN ON THE BLOOD SUGAR CURVE

Case Number	Name	Diagnosis	Stage of Disease	Control Blood Sugar	Blood Sugar after Subcutaneous Injection of 1 Mg. Epinephrin						
					1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	5 Hrs.	6 Hrs.	7 Hrs.
1	P. M.	Pneumonia	Acute	0.120	0.166	0.206	.....	.....	0.166	.....	0.136
2	C. F.	Pneumonia	Acute	0.103	0.130	0.141	.....	.....	0.118	.....	0.096
3	M.	Pneumonia	Acute	0.116	.....	0.200	0.142	0.153	0.156	0.142	.....
4	F. R.	Pneumonia	Moderate	0.096	0.134	0.108	0.102	.....	0.086	.....	0.097
5	E. M.	Influenza	Acute	0.105	.....	0.223	.....	0.133	0.100	.....	.....
6	C. S.	Influenza	Acute	0.097	.....	0.137	.....	0.109	0.096	.....	.....
7	M. L.	Influenza	Moderate	0.081	0.096	0.090	.....	.....	0.081	.....	0.084
8	T. J.	Influenza	Moderate	0.104	0.157	0.107	0.092	.....	0.098	.....	0.097
9	P. B.	Normal	.....	0.086	0.120	0.161	0.081	.....	0.079	.....	.....
10	C. H.	Normal	.....	0.087	0.206	0.169	0.082	.....	0.078	.....	.....
11	A. R.	Mumps	Acute	0.104	0.157	0.110	0.092	.....	0.096	.....	0.097

cases. We followed the blood sugar curve over a long period, often to the seventh hour without food ingestion during the period of observation. Our results are recorded in Table 3.

Cases 1, 2 and 3 show a distinct delay in the return of the blood sugar to normal. In Case 1 it had not returned to normal seven hours after the injection. In Case 2 it had not reached normal at the fifth hour, and in Case 3 it is not back to normal at the sixth hour. It may

be significant that Case 4 is practically back to normal at the third hour. Undoubtedly, had an observation been made, it would have been back to normal at the fourth hour. This was a case of pneumonia, but the patient was not acutely prostrated as were the other three. Cases 5 and 6, uncomplicated influenzas, show some delay, but it is not as marked as is that of the pneumonias, whilst Cases 7 and 8, influenzas of only moderate degree, in which the prostration was only slight, show blood sugar curves closely simulating those obtained in normal cases.

We believe these sustained blood sugar curves support the idea that endocrinal dysfunction is a factor in influenza and influenzal pneumonia, and that the degree of endocrinal involvement is proportional to the prostration. The long sustained blood sugar curves obtained by Hamman and Hirschman were observed only in endocrinal disturbances, hyperthyroidism and diabetes.

TABLE 4.—THE EFFECT OF GLUCOSE INGESTION ON THE BLOOD SUGAR CURVE

Case No.	Name	Diagnosis	Stage of Disease	Weight of Patient	Grams of Glucose Given	Control Blood Sugar	Blood Sugar after Ingestion of Glucose				
							1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	5 Hrs.
1	M. L.	Pneumonia	Acute	137	125	0.143	0.248	.....	0.179	.....	0.128
2	F. B.	Pneumonia	Conv.	80	75	0.107	0.152	.....	0.107	.....	0.107
3	W. R.	Influenza	Acute	162	150	0.097	0.246	.....	0.118	.....	0.104
4	M. S.	Influenza	Conv.	110	100	0.106	0.218	.....	0.127	.....	0.099
5	R. M.	Influenza	Conv.	155	125	0.116	.....	0.159	0.132	0.121	0.119
6	E. M.	Influenza	Conv.	112	100	0.104	.....	0.225	0.162	0.121	0.107
7	P. B.	Normal	.....	165	150	0.114	0.139	0.110	0.110		
8	C. H.	Normal	.....	137	125	0.093	0.110	0.098	0.096		

C. Blood Sugar Curve After the Ingestion of Glucose: Janney and Isaacson<sup>25</sup> call attention to the diagnostic value of the blood sugar curve following the ingestion of glucose in diseases of endocrinal origin. They took the blood from a fasting patient for a control, and gave 1.75 gm. of glucose per kilogram of body weight. The blood was then analyzed for sugar at stated intervals. In a series of normal persons, they found that the glucose content of the blood returned to normal in two hours. In a patient with an endocrinal disturbance, the curve did not return to normal until the end of the third and sometimes of the fourth hour. They concluded that this delayed blood sugar excretion curve is significant of an endocrinal dysfunction of some character, though not indicative of any particular gland. We have applied this test in six influenza cases and two control cases, with results as shown in Table 4. The weight of the person and the amount of glucose ingested are indicated. We were not able to follow the exact directions given by Janney and Isaacson, because only reported weights of the patients could be obtained.

It will be seen from this series of observations that the normal blood sugar curve appears in only one of the six cases (Case 2), and that prolonged curves are present in the other five. Fourth hour observations were made in only two cases (Cases 5 and 6). In neither of these had the curve returned to normal. Normal blood sugar values were obtained in all cases at the fifth hour. Case 2, which presents a normal curve, was a patient convalescing from pneumonia. His temperature, pulse and respiration had been normal for three weeks. He had a bad cough and a few moist râles. Aside from this he was well and was in no way prostrated. We would expect this patient to show a normal blood sugar curve. This fact seems to show that the endocrinal dysfunction returns to normal completely during convalescence or when the asthenia disappears. It is important to state that this patient had a severe pneumonia and at that time was prostrated very markedly.

The variations from normal which we have observed in the blood sugar curve after the ingestion of glucose coincide with the results of Janney and Isaacson, and lend further support to the idea that influenza affects the internal secretory system.

*Therapeutics of Epinephrin in Influenza.* — The French school, notably Sergent, Josue, Netter and Renon, advocate the use of epinephrin in influenza by the subcutaneous and intramuscular routes, the latter having the preference because they found that the subcutaneous method depressed the patient. We used the intramuscular method entirely. Some patients received 10 minims every four hours, four times daily; other patients received 15 minims every four hours, four times daily. These patients were in the hospital during the early part of the epidemic. Almost invariably the patient reacted with palpitation, complained of nervousness, slight headache and increased lassitude, and, occasionally, marked twitching occurred. The temperature was raised slightly and the pulse and respiration generally showed a marked increase. In one case, in which the asthenia was marked, the blood pressure was definitely raised after prolonged administration of epinephrin. We came to the conclusion that epinephrin so administered at least was of little, if any, benefit, and discontinued its further use. Possibly the proper method of administering epinephrin has not yet been found.

#### CONCLUSIONS

1. Necropsy reports reveal hypoplasia of the suprarenals and evidence of suprarenal dysfunction.
2. The occurrence of suprarenal dysfunction in influenza and influenzal pneumonia may be regarded as indicated by the cardinal symp-

toms, the characteristic rise in blood pressure following the prolonged administration of epinephrin, and the prolonged blood pressure curve following the administration of epinephrin.

3. That an endocrinal disturbance is present in influenza and influenzal pneumonia is further suggested by prolonged blood sugar curve after injection of epinephrin; prolonged blood sugar curve after ingestion of glucose.

4. Hypoglycemia is not present in influenza and influenzal pneumonia as has been found to be the case in some diseases of endocranial origin.

5. If epinephrin is of any use in the treatment of the symptoms of suprarenal dysfunction, the proper method of administering the epinephrin seems not yet to have been found.

## AUSCULTATORY PHENOMENA OF THE HEART IN NORMAL MEN AND IN SOLDIERS WITH IRRITABLE HEART

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In the examination of men in the army for cardiovascular diseases, one is continually impressed with the frequent occurrence of certain adventitious sounds and murmurs of the heart in men of apparently robust physique. The problem of determining whether certain sounds or murmurs other than the conventional "lub-dupp" of the heart-sounds should be considered significant of heart disease or as merely accidental phenomena belonging to normal hearts is often perplexing. It is a much more simple task for most of us to classify properly a mixed group of organic cardiac lesions, probably because physical diagnosis is taught in medical schools largely from the study of pathologic conditions, and also because it is seldom possible to study normal hearts in large enough numbers to allow us to clarify our ideas as to which deviations from the usual should be considered normal and which pathological.

It is often advised that the diagnosis of organic heart disease be made only in the presence of cardiac hypertrophy, but we are often forced to the conclusion that such a rule does not hold good. For example, the diagnosis of aortic insufficiency is made for us when we hear a murmur of a certain type in diastole; yet one sees many soldiers with aortic insufficiency who present no demonstrable hypertrophy of the heart nor, indeed, any other secondary sign of the lesion. These men, also, frequently do not present symptoms, their condition being discovered accidentally in the demobilization, after they have done full duty.

If aortic insufficiency exhibits itself by the presence of only a murmur, without other cardiac signs or cardiac symptoms, why should not any other cardiac lesion do the same? The murmur of aortic insufficiency is not simulated frequently enough by accidental or cardio-respiratory murmurs to warrant question of the diagnosis, provided the typical murmur is present. The chief difficulty in the diagnosis of other valvular lesions lies in the fact that the murmurs resulting from these lesions may be duplicated almost exactly by murmurs from other causes. The diagnosis of mitral insufficiency, for example, is often very difficult because of the variety of systolic murmurs that

may be heard over or about the apex of the heart; hence we often find ourselves obliged to decide the significance of a single cardiac phenomenon on its own merits.

This report is made for two purposes: first, to show the incidence of deviations from the usual found in heart examinations of healthy soldiers who have done duty, and second, to discuss the physical examinations of men with irritable heart in the light of the above data.

Thayer<sup>1</sup> has given his experience bearing on diagnosis of these phenomena. He describes as normal phenomena: (1) The systolic click; (2) the third heart sound; (3) basic systolic murmurs; (4) apical systolic murmurs which disappear in the erect posture, and (5) the cardiorespiratory murmurs. He classifies extrasystoles and reduplication of the second sound at the pulmonic area as phenomena the significance of which must be determined for the individual case. He considers them of no especial significance per se, but as confirmatory evidence of cardiac disease in certain cases in which other signs are present.

At U. S. Army Hospital No. 9 the most careful physical, laboratory and electrocardiographic examinations of soldiers with irritable heart have failed to show any organic defect in the heart. These men are, however, peculiarly apt to present adventitious phenomena in the heart, especially cardiorespiratory and "accidental" murmurs. The question arises whether such murmurs are purely accidental findings, or whether they have some bearing on the condition of the individual. Lewis,<sup>2</sup> after careful study of men with this complaint in the British Army, considers that the presence of cardiac systolic murmurs means nothing per se in irritable heart. He found that 58 per cent. of the men with this condition who were without murmurs were unfit for duty, whereas only 51 per cent. of the men with murmurs were unfit for duty. He found that 42 per cent. of all men with "soldier's heart" showed systolic murmurs. Possibly, the most direct way to approach this problem is by the examination of normal soldiers who have done duty. If all the physical findings of irritable heart are common in normal individuals, the inference should be allowed that such findings probably have no bearing on the condition of irritable heart.

While examining officers and men of the Air Service at Garden City for demobilization, I had the opportunity of studying and classifying auscultatory phenomena as they occurred in the hearts of healthy

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1. Thayer, W. S.: "Observations on some of the commoner deviations from the ordinary met with in the examination of the heart of supposedly normal individuals," *Med. Rec.* **91**:617 (April), 1917.

2. *Med. Research Committee Rep.*, 1918.

men who had done full army duty. These men were almost uniformly between 18 and 31 years of age, the average probably falling below 25. Five hundred men were studied in detail. The results of this examination are given in the table below. Two or more adventitious findings were not infrequently present in the same individual; the total number of men who showed one or more of the given sounds or murmurs was, therefore, somewhat less than the sum of murmurs and sounds found. In each case the man was examined in the standing, the supine and the left lateral posture. The effect of respiration on each murmur or sound was also studied.

## AUSCULTATORY PHENOMENA OF 500 SUPPOSEDLY NORMAL HEARTS

	No. Cases	Per Cent.
Third heart sound .....	118	23.6
Reduplication of first sound at apex .....	16	3.2
Systolic apical click .....	2	0.4
Systolic murmur at apex present* in recumbent posture, absent in erect posture .....	65	13.0
Cardiorespiratory systolic murmurs limited to inspiration:		
At apex .....	16	3.2
At conus arteriosus .....	4	0.8
At aortic area .....	3	0.6
Cardiorespiratory systolic murmurs present in both inspiration and expiration:		
At apex .....	13	2.6
At conus arteriosus .....	5	1.0
At aortic area .....	2	0.4
Accidental systolic murmurs:		
At conus arteriosus .....	70	14.0
At aortic area .....	31	6.2
Cardiorespiratory diastolic murmurs:		
Near aortic area .....	3	0.6
Near conus .....	1	0.2
Near apex .....	0	0.0
Extrasystoles .....	9	1.8
Reduplicated second sound at conus area .....	23	4.6

*The Third Heart Sound.*—On this point there is nothing to report, except the figures for healthy men in the third decade. Only well-marked third sounds are included. Third sounds heard for two or three beats after change of position and those heard for an occasional couple of beats during a certain phase of respiration were not recorded. Moreover, well developed men probably do not show the third heart sound so frequently as do individuals with thin chest walls. These two factors probably made the percentage lower than that reported by Thayer,<sup>3</sup> who heard this sound in 50.9 per cent. of individuals in the third decade of life. The sound was most often heard best with the patient in the left lateral posture, though occasionally it was loudest in the supine position. It was seldom heard distinctly in the erect posture. In no case was the sound associated with signs or symptoms of cardiac disease, and it was considered to be uniformly without significance.

3. Further Observations on the Third Heart Sound, Arch. Int. Med. 4:297 (Oct.), 1909.

*Reduplication of the First Sound at the Apex.*—In this group are included cases in which two distinct and almost equally intense sounds occur at the very beginning of systole. Morris and Friendländer<sup>4</sup> have recently described this phenomenon in soldiers and have noted that it is sometimes associated with a short presystolic thrill and sometimes with a palpable double systolic impulse. They have pointed out that this condition may readily give rise to the erroneous diagnosis of mitral stenosis, and they consider the reduplication in itself as of no significance. They noted that it was heard best in the erect posture, disappearing entirely or being much diminished in the supine position. It is often very difficult to determine which of the two sounds is the louder; indeed, in some cases it is impossible to decide by auscultation. The reduplication bears no resemblance to the presystolic gallop rhythm nor to an auricular contraction; it is not similar to the "impure" or "flapping" first sounds. The two sounds are both forceful and distinct. There is, however, one distinctive quality of this type of reduplication, it either disappears entirely or diminishes in intensity when the subject assumes the supine position, being heard best with the subject erect.

In the series of sixteen cases recorded above, the reduplication disappeared entirely in ten cases when the man lay on his back. It has always impressed the writer as being due to the impact of the heart against the chest wall as it undergoes contraction and torsion during systole. This hypothesis is supported by the disappearance or diminution of the phenomenon in the supine posture, when the heart would tend to drop back from the chest wall. Occasionally the reduplication is accompanied by a distinct thrill; this occurred in two of the sixteen cases reported above. It has always seemed to the writer to accompany the systolic impulse, rather than to be really presystolic in time. The signs of this condition are radically different from those of mitral stenosis in the following respect. It is well known that the signs of mitral stenosis are usually maximal in the recumbent or left lateral posture; in these positions the signs of simple reduplication of the first sound are absent or minimal.

*The Systolic Apical Click.*—This was described by Thayer<sup>3</sup> as a single click or rattle occurring immediately after the first sound at the apex, of a wooden quality, superficial and sounding near to the ear, and seeming to result from the shock of the first sound. This click was heard not infrequently by me in the examination of some 15,000 soldiers. In the group of 500 reported here it occurred twice. It was

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4. The Significance of Presystolic Thrills in the Examination of Soldiers, J. A. M. A. **71**:375 (Aug.), 1918.

always superficial, and seemed to result from the movement of the heart in its sac. It has been heard in early, late or mid systole. This click may become less distinct at the height of forced inspiration, but this is probably the result of the interposition of lung tissue from inspiration, for the sound fails to disappear at any phase of forced inspiration or expiration. It does, however, in some cases entirely disappear when the subject is supine, which strengthens the impression that it is an accidental extra-cardiac phenomenon.

*Heart Sounds at the Left Sternal Border.*—Blumer<sup>5</sup> described a crunching or scratching quality to the heart sounds in the region of the lower left sternal border. It is a common phenomenon of the normal heart, and may be observed in most hearts, in the leaning forward position particularly. Blumer considers that it probably originates in the tissues overlying the heart. He pointed out that the crunching quality is uninfluenced by respiration, that it is most marked in the leaning forward position, and that, in many cases, it is little or not at all influenced by change of position.

This phenomenon has been observed commonly by me in normal soldiers and in men with irritable heart. In two instances the scratching quality was drawn out and assumed the character of a true murmur. One of the cases occurred in a man with irritable heart, with vigorous heart action, who had been sent into the hospital with a diagnosis of mitral insufficiency. Examination showed the first sound at the lower sternal border prolonged into a definite superficial, squeaking murmur. This murmur, or squeak, was loudest in the leaning forward position. It was not influenced by respirations, but it was entirely absent when the man lay on his back. The location and characteristics of this murmur were so similar to the "crunching" quality of normal heart sounds, that it seemed almost surely to be a superficial friction sound of either the normal pericardium or of some of the other extra-cardiac superficial structures. Its accentuation in the leaning forward position was probably due to the friction of the heart against the chest wall, and its prompt disappearance in the recumbent posture probably due to the release of this friction.

In another case, a healthy nurse, with a perfectly normal heart and without cardiac symptoms, there was heard a short, early, very superficial, diastolic murmur along the lower left sternal border. It had none of the blowing quality of the murmur of aortic insufficiency, and it was obviously a superficial short "crunch" after the second sound, apparently due to the drawing out of the scratch of the second sound

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5. A Note on the Normal Peculiarities of the Heart Sounds in the Region of the Sternum, Arch. Int. Med. 14:605 (Oct.), 1914.

usually heard in this area. This murmur was not influenced by respiration; it was increased in the leaning forward position, and was least intense in the recumbent (supine) posture. This is a very rare phenomenon, and I did not notice such a murmur in the examination of about 15,000 soldiers. Nevertheless, on account of its occurrence in diastole and its position at the left sternal border, such a murmur might easily pass, on casual examination, for one of aortic insufficiency, and for this reason it is recorded.

It was noted that individuals who had "flat" chests, and especially those who had a tendency to "funnel-chest," usually showed the "cruch" to an unusual degree.

*The Systolic Apical Murmur in the Recumbent Posture.*—This is a common phenomenon, now widely recognized as an accidental murmur met with in normal hearts. It is second only to pulmonic systolic murmurs in frequency (see table). In the recumbent posture, the murmur has the quality of that of mitral insufficiency, but it differs from the murmur of true insufficiency by disappearing in the erect posture. It is not radically affected by respiration, as are the cardiorespiratory murmurs. It is never associated with cardiac hypertrophy or other secondary signs of cardiac disease in a causative rôle.

*Cardiorespiratory Murmurs Limited to Inspiration.* These murmurs are heard frequently, and should be recognized readily. If a murmur is limited to inspiration it may be classed at once in the cardiorespiratory group. They are most common at or about the apex, being often heard over the lingula pulmonalis or over the lung just outside the apex. They usually disappear promptly if a deep breath is taken and held at the end of inspiration. The explanation of this is simple, for the murmur is an intensification of the inspiratory lung sound, and when the lung is fixed at the end of inspiration it is not readily affected by the movements of the heart. Cardiorespiratory apical murmurs are most often loudest in the erect posture, thus differing from the accidental apical murmurs described in the preceding paragraph. They may disappear promptly when the subject assumes the supine position, probably from the dropping back of the heart and the release of pressure from the overlying lung. However, when the man assumes the left lateral position, cardiorespiratory murmurs are apt to reappear, probably because the heart swings toward the left and impinges on the lung again. Cardiorespiratory murmurs are often heard well in the left back, in which case the murmur seems to be formed in the lung behind the heart, and not to be transmitted from the apical region; cardiorespiratory murmurs are apt to be louder in the back than in the left axilla, probably for this reason.

*Cardiorespiratory Murmurs Heard in Both Inspiration and Expiration.*—These murmurs follow all the general rules of cardiorespiratory murmurs, as described in the preceding paragraph, except that they occur in both phases of respiration, usually disappearing when the breath is held at the end of full inspiration. The two varieties are almost equally common. One of the loudest murmurs heard in the cardiac wards of our hospital occurred in a man with irritable heart and belong to this group of murmurs. In the erect posture it was loud, rough, and lasted throughout systole; it was heard in the back, and occurred in both phases of respiration. When the man leaned forward, however, the murmur disappeared entirely, and it was also entirely absent in the supine position. It was clearly a cardiorespiratory murmur, for it could be made to occur even in the recumbent position by having the man take deep breaths; such a procedure would increase the volume of lung over the heart and restore the intimate contact of heart and lung. The disappearance of the murmur in the leaning forward position was interpreted as probably being due to the heart dropping forward and pushing the lung lappet aside.

*Systolic Murmurs at the Base of the Heart.*—These murmurs are discussed freely in the literature, and there is nothing to note except their frequency (20.2 per cent. at the aortic and pulmonic areas together). In the study of the 500 normal men, a heading had been set aside for "pulmonic systolic murmurs limited to expiration," as the elder Janeway<sup>6</sup> has pointed out the marked effect of forced expiration upon the pulmonary systolic murmur, and the writer had previously seen instances of this murmur's occurring only during expiration. However, in the group of men examined, no such case presented itself, though the murmur is almost always loudest after forced expiration. The murmurs noted at the aortic area were, in each case, similar to the pulmonic systolic murmurs in quality; there was no reason in any case to suspect valvular disease or aortitis, and the murmurs were considered as probably accidental.

*Cardiorespiratory Diastolic Murmurs.*—Occasionally superficial, to and fro, systolic and diastolic murmurs occur near the borders of the heart. Diastolic murmurs of this type may be distinguished readily from those of aortic insufficiency. The murmur may be limited to inspiration, in which case it may be classed at once in the cardiorespiratory group. It rarely occurs just at a valve area, and I have never heard it in the third left interspace, where the murmur of aortic insufficiency is usually maximal. In the four cases tabulated above it was always found just beyond the valve areas; in three cases it was

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6. Discussion of Thayer's Paper, Trans. Assn. Amer. Physicians, **21**:61, 1906.

heard over the root of the aorta and in one case over the root of the pulmonary artery. These murmurs always disappear promptly at the end of forced inspiration. They are superficial, lack the blowing quality of the aortic insufficiency murmur, and are not transmitted. On hypothetical grounds, one might expect that a movement of air currents in the lungs could occur from relaxation of the heart and aorta in diastole as well as from the contraction of the heart and distention of the aorta in systole. Yet the occurrence of diastolic cardio-respiratory murmurs is not generally recognized. Almost certainly, however, any one can convince himself that they do occur by examining a sufficient number of healthy men. Such murmurs will seldom offer any serious complication, to a careful observer, in the diagnosis of aortic insufficiency, but the possibility of their occurrence should be borne in mind.

*A Diastolic Murmur of Unknown Origin.*—An endocardial murmur at the base of the heart or along the left sternal border that does not indicate aortic insufficiency is extremely rare. So far as I know, no such case was noted in the examination of about 15,000 soldiers. Cabot<sup>7</sup> described the cases of two medical students with "perfectly healthy hearts, who were able, by prolonged holding the breath, to produce a short, high pitched diastolic murmur, best heard in the second and third left intercostal spaces and ceasing as soon as the breath was let out." A patient seen recently at this hospital presented signs very similar to those described by Cabot. This man had a surgical and not a medical complaint, and the murmur was found accidentally. He had been a long distance runner. He gave no history of rheumatic fever, syphilis, or other acute infection of importance, and the Wassermann reaction was negative. He had no cardiac symptoms. The heart was normal, but he showed a diastolic murmur along the left sternal border from the pulmonic area to about the fifth rib. It seemed to be an endocardial murmur, and it had the quality of the murmur of aortic insufficiency. It varied somewhat, in an inconstant way, on change of posture, but its most striking characteristic was the effect of respiration on it. When the man took a deep inspiration and held his breath, there was heard a high pitched, blowing, rather intense diastolic murmur along practically the whole left sternal border. As soon as he began to expire, however, the murmur began to decrease in intensity, and at the end of expiration, when the murmur of aortic insufficiency is loudest, this murmur was entirely absent. This case seems to be analogous to the two cited by Cabot, except that this murmur occurred during natural breathing, and would have com-

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7. Physical Diagnosis, Ed. 6, William Wood & Co., New York, 1915.

pelled the diagnosis of aortic insufficiency were it not for its peculiar behavior at various phases of respiration. The cause of this murmur is unknown; in this case, it was not associated with any signs of heart trouble nor with any symptoms.

*Extrasystoles.*—Occurring in only 1.8 per cent. of the men examined for demobilization, extrasystoles are less common than they are in the examination of new recruits. They were not numerous in any case of the above group, and they never occurred with sufficient regularity to produce bigeminal or trigeminal rhythm. The heart was negative on physical examination in each case, and in no case were there any symptoms except palpitation.

*Reduplication of the Second Sound at the Pulmonic Area.*—This phenomenon was noted in 4.6 per cent. of the 500 men examined, and no significance for such reduplication could be found.

In the study of irritable heart at this hospital, no sounds or murmurs of the heart have been found which differed in any essential particular from the various types of murmurs described above as occurring in healthy soldiers who have done duty. There are numerous cardiorespiratory and accidental murmurs among men with irritable heart, but in view of the unusual vigor of the heart's action in such cases, it would be surprising if this were not the case.

#### SUMMARY

1. A report is made of the various adventitious sounds and murmurs found in the examination of the hearts of 500 supposedly healthy soldiers who had done army duty.

2. A few unusual murmurs and sounds found in the examination of almost 15,000 supposedly healthy soldiers are recorded.

#### CONCLUSION

Murmurs and adventitious heart sounds probably have only an accidental relationship to the "irritable heart of soldiers."

## INFLUENZA AND NEUROSYPHILIS \*

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Influenza has long been recognized as a precipitating factor in the production of mental disease. Although a few authorities maintain that it may be the sole cause of certain psychoses, probably no one today believes that influenza is ever the sole cause of general paresis. It has been observed, however, that neurosyphilis has sometimes appeared clinically for the first time after attacks of influenza, and this evidence makes the influence of influenza in the etiology of neurosyphilis a legitimate point of inquiry.

Even in the pre-Wassermann days influenza was, strangely enough, not generally considered as among the possible causes of general paresis. After the epidemic of 1890 a number of instances of the precipitation of neurosyphilis by influenza were reported, and these, along with analogous cases of epilepsy, chorea, etc., were styled by Kalischer,<sup>1</sup> Kirn<sup>2</sup> and others, "Pseudoinfluenza psychoses." The implication was that the influenza acted merely as an incidental precipitating factor and might be replaced by any other form of infection. Attention has been called to this repeatedly, and Duke<sup>3</sup> emphasizes the importance of peridental infections. It would seem that simultaneous infective processes may cooperate in their attacks on the system, producing a clinical picture, however, wholly resembling the usual results of the one assailant. At least, this is apparently the result in the case of the interaction of neurosyphilis and influenza.

A considerable number of instances of neurosyphilis appearing first after influenza were studied in the recent epidemic in the series reported from the Boston Psychopathic Hospital. In practically all of

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\* A contribution from the Boston State Hospital, Psychopathic Department, Series of 1919. This is the third of a series of papers on Psychoses Associated with Influenza. The first appeared in J. A. M. A. **72**:235 (Jan. 25), 1919. The second has been accepted for publication in the Archives for Neurology and Psychiatry.

1. Kalischer: Arch. f. Psychiat. **29**:

2. Kirn (insists on this point in various of his several writings on influenza, e. g.), Ueber Influenza Psychosen, München med. Wchnschr. **37**:299, 1890. Die nervösen und psychischen Störungen der Influenza, Samml. klin. Vortr., n. F., Leipzig, No. 23, 1891. Die Psychosen der Influenza, Allg. Ztschr. f. Psychiat. **47**: 1, 1891.

3. Duke, W. W., Oral Sepsis in its Relationships to Systemic Disease, St. Louis, 1918.

these cases there was close chronologic association of the influenza and the appearance or aggravation of mental (neurosyphilitic) symptoms.

The question is immediately asked as to the relationship of the influenza and the neurosyphilis. Is it more than that of chronologic sequence, more than coincidental? Is it a further manifestation of the neurotoxic potentialities of the influenza toxin? Is the effect confined to augmentation and never to alleviation of neurosyphilitic symptoms? To all of these queries the evidence at hand favors an affirmative answer.

#### LITERATURE

Of the literature concerning the relation of influenza to neurosyphilis, there is a remarkable paucity. Leichtenstein,<sup>4</sup> in his celebrated monograph covering the subject intensively, confines his consideration of neurosyphilis to this sentence: "The first signs of 'general paralysis' have often followed influenza (Althaus<sup>5</sup>)."<sup>6</sup> Leledy<sup>6</sup> lists three cases, one of his own, one quoted briefly from Kraepelin, and a third from Magnan's clinic, reported by Rabinovitch. All three are cases of neurosyphilis paretica, appearing in an acute form first after an attack of influenza. Mills<sup>7</sup> and Knapp<sup>8</sup> concluded that at least as far as paresis was concerned, "influenza only reveals old syphilitic processes or exaggerates some troubles which previously had passed unperceived."

Krypiakiewicz<sup>9</sup> cited a case "in which" (comments Espagnol<sup>10</sup>) "the relation of cause and effect between general paresis and influenza seems very close."

Erb,<sup>11</sup> in discussing tabes, wrote that ". . . it is certain that if influenza be added to tabes it decidedly aggravates the affection and accelerates its cause, and there is no doubt that the first tabetic symptoms occasionally appear after an attack of influenza." But he appends a note of skepticism as to the possibility of influenza as a sole cause.

But, in general, the literature is very scant, probably the most so of any phase of the psychiatric side of influenza. Bossers,<sup>12</sup> in his

4. Leichtenstein, O., *Influenza*, Nothnagel's *Encycl.* **103**:

5. Althaus, Am., J. M. S. 361, 1892.

6. Leledy, A., *La Grippe et Alienation Mentale*, Paris, 1891.

7. Mills, Trans. Phila. Co. Med. Soc., 1892.

8. Knapp, P. C., Boston M. & S. J., 1891.

9. Krypiakiewicz, *Jahrb. f. Psychiat.*, **10**:

10. Espagnol, J., *Contribution a l'étude des rapports de la grippe et du système nerveux*, Toulouse, 1895.

11. Erb, *Deutsch. Klinik*, edited in English by Church, Appleton's *Modern Clinical Medicine*, New York, 1908.

12. Bossers, A. J., *Die Geschichte der Influenza und ihre nervoessen und psychiatrischen Nachkrankheiten*, Leiden, 1894.

excellent monograph, does not mention it. No articles dealing directly with the subject were found in a search of the Surgeon-General's Index, the Index Medicus, and the bibliographies of such monographs as those of Bossers,<sup>12</sup> Bonhoeffer,<sup>13</sup> Leichtenstern,<sup>4</sup> Espagnol,<sup>10</sup> etc. It is not mentioned in Nonne's<sup>14</sup> authoritative work, nor by Southard and Solomon<sup>15</sup> in their case-history book, and these are certainly our best modern treatises on neurosyphilis.

The following case histories of neurosyphilis were taken from the series of cases of mental disease associated with influenza observed at the Boston Psychopathic Hospital in the recent epidemic.<sup>16</sup> They fall logically into four groups, with a fifth hypothetical group not illustrated. The groups have, as a basis of classification, the degree of pre-existent symptomatology, and are explained in the text.

### CASE HISTORIES

**GROUP 1.**—Cases in which there were no symptoms of neurosyphilis whatever until after the attack of influenza.

**CASE 1.**—*Normality + (Latent Syphilis) + Influenza = General Paresis.* Male, aged 46, single, contracted influenza followed by irritability, delusions, amnesia, dysthymia. The serology and neurology was that of neurosyphilis paretica.

(It is certain that not many years ago the circumstantial evidence of such a case as this would have been accepted as proof of the possibility of a non-syphilitic etiology for general paresis.)

*Family History.*—Negative.

*Past History.*—Negative. The only symptom of any kind prior to an attack of influenza had been the complaint of fatigue during the four preceding summers. He used no alcohol or tobacco.

*Present Illness.*—He contracted influenza, which became rather severe in degree but terminated in four days. He arose from bed, but evidently suffered a relapse and returned to bed again, after two weeks. Two days following this he was delirious. He is also described as being irritable and negativistic, and announced that the Blessed Virgin Mary was going to tell him what to do. There is a vague account of two seizures. He was then brought to this hospital.

*Mental Examination.*—His consciousness seemed entirely clear. He was correctly oriented, but with a grossly defective memory for both recent and remote events. He presented fleeting persecutory somatic delusions, fearing that he was dying, that he had been poisoned, etc. No hallucinations were elicited. His emotional tone showed instability and at times a tendency toward agitated depression. There was a disruption of thought processes and a decrease of motor activity.

*Physical Examination* showed no defect of special senses or of epicritic or protopathic sensations. Deep sensations were somewhat impaired. The pupils

13. Bonhoeffer, Aschaffenburg's Handb., Leipzig & Vienna, 1915. Menninger, Karl A., Psychoses associated with influenza, J. A. M. A. **72**: 235 (Jan. 25), 1919.

14. Nonne, Syphilis of the Nervous System (translated by Ball).

15. Southard & Solomon, Neurosyphilis, Boston, 1917.

16. Menninger, Karl A., Psychoses associated with influenza, J. A. M. A. **72**: 235 (Jan. 25), 1919.

were contracted and reacted neither to light nor accommodation. Tremor of facial muscles, tongue and extended hands was present. The knee jerks were equal and active. There was slight swaying in the Romberg position. The abdominal and cremasteric reflexes were absent.

The blood serum Wassermann test was positive. The spinal fluid showed an increase of albumin, globulin, four cells and a unique gold sol reaction of 5555555555, with a positive Wassermann reaction.

*Diagnosis.*—Neurosyphilis paretica (general paresis). The man was committed.

*CASE 2.*—*Normality + (Syphilis) + Influenza = Cerebral Syphilis.* Male, aged 31, salesman, who had had chancre eleven months previously, now had a severe attack of influenza, with "delirium" and seizures. The spinal fluid findings were typical of paresis, except for a negative Wassermann reaction.

*Family History.*—A brother is considered "mentally undeveloped;" otherwise the family history is entirely negative.

*Past History.*—This is entirely negative, except that he formerly used considerable alcohol, but was never drunk or hallucinated, and had been for six months totally abstinent. He had been quite successful in business, and earned a substantial salary.

*Marital History.*—He was married eight years prior to admission; his wife is living and well but childless because of a hysterectomy done prior to marriage.

*Present Illness.*—He admitted that despite his happy married life, he had been on several occasions unfaithful to his wife. Three years previously he had had gonorrhea and one year—he thought precisely eleven months—previously he had had a running sore about the size of a dime on his penis, which was not particularly painful or indurated. It disappeared after about three weeks and was not followed by adenitis, pharyngitis or dermatitis. He did not consult a physician. The scar remains.

For the past five years he has had "grippe" every year. December 12, 1918, while traveling across country by automobile, he was taken with a severe headache and general malaise. He arrived home at 10 p. m. with a temperature of 103.5 F. A physician was called and diagnosed his case as one of influenza.

December 15 (third day) he had "what appeared to be a convulsion" (physician's written statement). Involuntary urination occurred, and "he seemed to be dying." The attack lasted about five minutes. He had no memory of it afterward, and asked his wife why she appeared so frightened. Later in the day he remarked to her, "I think I fainted again," but there was no proof of this.

December 19 (seventh day) his temperature fell to normal. In the morning he related some bad dreams of the night before, and later in the day he spoke queerly and somewhat incoherently. At 7 p. m. he had another convulsion, "all his limbs contorting, he frothed at the mouth and beat the air with his hands." He appeared frightened, and what he said could not be understood. "His wife had great difficulty in holding him in bed. The attack lasted about five minutes."

Following this attack he did not regain consciousness fully, but remained "stuporous and queer," obeying a few commands, signalling for the bedpan and keeping himself covered, but unable to speak intelligently.

December 17 (ninth day) he entered the hospital in a state of delirium, disoriented and oblivious to external stimuli. Pupils then reacted poorly to light. He muttered an unintelligible jargon and tossed about on his bed incessantly.

December 18 his condition was unchanged during the forenoon. About 10 a. m. a lumbar puncture was done, and thereafter he became quite clear, approximately oriented and, on the whole, fairly normal mentally.

December 19 (eleventh day) he was quite clear until about 10 a. m. His mentality became greatly retarded, then completely blocked. This was followed by a severe seizure, tonic convulsions with cyanosis, champing bloody froth and

gross tremor, succeeded by clonic spasms for several minutes and then stertorous coma.

For a short time afterward he was in a typical "twilight state," fabricated freely, and was completely disoriented. Fifteen minutes later he was entirely clear and entirely amnesic for the seizure. The same afternoon he had another seizure of much less severity.

December 20 and 21 he remained entirely clear. A routine mental examination was in all respects entirely negative except for an undue euphoria. He begged with spirited earnestness to go home for Christmas, talked somewhat too loudly, but passed for entirely normal with the whole staff. He was discharged against the advice to his wife on December 22. No more seizures occurred.

*Physical Examination.*—Pupillary reaction was sluggish to light on admission, but subsequently responded normally. All reflexes were normal, and there were no abnormal physical or neurologic findings. There was a scar, like that of a chancre, on the glans penis. The blood pressure was 120-70.

*Laboratory Findings.*—The urine was negative. Blood examination showed 4,700,000 erythrocytes, 12,900 leukocytes; hemoglobin, 80 per cent. The differential white count was normal. Spinal fluid examination showed globulin 2 plus, albumin 2 plus, forty-one cells, of which nine were small and eighteen large lymphocytes, and fourteen were polymorphonuclear cells. The gold sol reaction was 5554321110. Wassermann tests of spinal fluid and blood serum were negative. Diarsenol G., 0.3 gm. had been given on the fifth day. The psychometric rating on the sixth day was 11.4 years.

*Diagnosis.*—Neurosyphilis (cerebralis: ? paretica).

CASE 3.—*Normality + (Latent Syphilis) + Influenza = General Paresis.* The patient was a man, aged 40. His wife was known to have had syphilis. No nervous manifestations were noted until after an attack of influenza. It was a typical paresis.

*Family History.*—This was negative, including the grandparents.

*Past History.*—Childhood was normal and his past life was negative. He had worked at various trades, but for fifteen years had conducted his own barber shop successfully. His wife had no miscarriages but is known to have had symptoms of syphilis many years previously. Two children are living and well. His habits had been quite good, and he was not alcoholic. There had been no serious illnesses.

*Present Illness.*—The man had been perfectly well in every respect. The previous year he had made more money than ever before, clearing over twelve hundred dollars from his barber shop and the few side affairs. He was extremely sociable, was perfectly well, both physically and mentally, according to well authenticated reports.

Some time in October he had had influenza for four days, his temperature rising to 103 F. It was not considered a particularly severe attack. He returned to work at once, but felt it a great exertion. From then on his wife noticed that he was unusually quiet and averse to conversation, which was quite in contrast to his former state. He began to show signs of memory difficulty and complained of it specifically. He did not, however, show any more severe symptoms for six months.

May, 1919, he was involved in some unjust legal difficulties. In the evening he came home very much disturbed. His wife states he was extremely restless, emotionally unstable, manifested twitchings in various parts of his body and constantly uttered complaints and laments. On the advice of his physician he came to the Psychopathic Hospital.

*Mental Examination.*—This showed pre-eminently a variable emotional tone, exhibiting in succession threats, laughter, tears and song. He was quite euphoric the greater part of the time, and alternated protestations of the excellence of

his health with complaints that he was still sick with the influenza from which he had never really recovered. There was marked psychomotor restlessness with great loss of attentive control. His memory was not markedly defective and hallucinations were not proved although both auditory and visual hallucinations were mentioned. Impairment of judgment was manifested in various minor ways; as, for example, in outbursts of profanity and obscenity before nurses, harangues of advice to other patients, threats of violent suicide, etc.

*Physical Examination.*—This was chiefly negative, including the routine neurologic tests. His pupils, however, reacted through a small arc, and there was considerable flattening out of the face.

*Laboratory Findings.*—The urine was negative. The blood Wassermann was negative. The spinal fluid was positive. Wassermann positive, with an increase of albumin and globulin, 163 cells, and a gold sol reaction typical of paresis (5 5 5 4 3 2 1 0 0 0).

*Diagnosis.*—Neurosyphilis paretica.

CASE 4.—*Normality* + (*Latent Neurosyphilis*) + *Influenza* = *General Paresis*. A man, aged 51, formerly a naval officer, after an attack of influenza, became "mentally foggy," demonstrated to be due to general paresis.

*Family History.*—Entirely negative.

*Past History.*—Chiefly negative. He was born in Maine, spent nearly 40 years at sea, part of the time as a high ranking naval officer. He had a common school education, and had had typhoid fever in childhood. He was mildly alcoholic, but had an excellent personality. He married at 32, and has one living child.

*Present Illness.*—November 6, 1918, he contracted influenza and was in bed for ten days. Absolutely nothing wrong had been noticed prior to that time. Thereafter a speech defect first appeared, then he was noticed to be becoming forgetful and irritable, and later destructive. He became more and more "foggy" and demented and was admitted to this hospital March 24, 1919.

*Mental Examination.*—At the time of admission he showed a grossly defective memory with absolutely no insight, and slight euphoria. His psychomotor activity was somewhat increased. He was quite restless a great part of the time, and occasionally he was destructive. There were no delusions or hallucinations. His thought processes showed retarded cerebration and considerable decimation. Most of the time he was disoriented.

*Physical Examination.*—This showed excellent development and nourishment, and no somatic pathology other than the neurologic examination, except what was diagnosed a gumma of the epididymis. Neurologic examination showed small pupils, which though equal did not react to light. There was a positive Romberg, with tremor of the tongue and hands, and all the deep reflexes were exaggerated. Ophthalmoscopic examination was negative. Speech defect was quite prominent.

*Laboratory Findings.*—The urine was negative, likewise the blood cytology. The blood Wassermann (three tests) was positive. Spinal fluid contained globulin and the albumin was much increased; eight cells. The gold sol test gave 5 5 5 5 5 5 5 4 2 2. The psychometric test gave a rating of 8.5 years.

*Diagnosis.*—Neurosyphilis paretica.

NOTE: He was immediately put under treatment. Received potassium iodid daily and diarsenol brand of arsphenamin bi-weekly. By the end of a month the tumor of the epididymis had decreased in size, speech had improved, he had begun to take a little interest in things and was generally regarded as having improved.

CASE 5.—*Normality* + (*Latent Neurosyphilis*) + *Influenza* = *General Paresis*. A male, aged 47, who, prior to an attack of influenza, had been perfectly well, thereafter developed symptoms of general paresis.

*Family History.*—Negative.

*Past History.*—He was born in Ireland, had a normal childhood, and has been fairly efficient economically since coming to the United States, earning twenty-five dollars a week as a waiter. He has been married for six years and has one child, with no miscarriages, no stillbirths and no dead children.

*Present Illness.*—It is established that prior to his influenza he was considered quite well and manifested no symptoms, mental or physical.

In October, 1918, he had influenza with a maximum temperature of 102.6 F. and was in bed for five days. He returned to work and was considered quite well for about a month, except that his wife thinks he was "nervous." January 1, however, he lost his position and from then on was noted by several people to be "not himself," and as he himself put it, in March, "all in." At this time he became disoriented and "childish" in his talk. He manifested difficulty in verbal expression of his ideas and suffered from insomnia. Memory defect was also noted.

*Mental Examination.*—On admission to this hospital, April 1, he was found to have a considerable bewilderment of thought processes, disorientation, memory defect, with an emotional tone of apathy and torpor. He lacked insight totally, and showed a speech defect.

*Physical Examination.*—This was chiefly negative. There was some evidence of chronic pneumonitis of the left upper lobe. Neurologically, the deep reflexes were all exaggerated and the periosteal reflexes were marked. Otherwise, the examination was negative.

*Laboratory Findings.*—The urine was negative. The blood cytology was normal. Serology showed a positive Wassermann. The spinal fluid findings were increased globulin and albumin, forty-eight cells, of which forty were small and eight large lymphocytes, and a positive Wassermann. The gold sol reaction was typically parietic, viz., 5555554420.

*Diagnosis.*—Neurosyphilis paretica.

**GROUP 2.**—Cases in which the previous symptoms were trivial, and not diagnostic, but in which typical and advanced neurosyphilis developed immediately after influenza.

**CASE 6.**—(Latent Neurosyphilis) = Paranoid Personality + Influenza = Advanced Neurosyphilis (paretica). A woman, aged 39, paranoid for several years, during convalescence from influenza suddenly manifested profound dementia (paralytica).

*Family History.*—Negative, including grandparents.

*Past History.*—Normal childhood and school life. Wages steadily advanced to \$183 a month. "She is the brightest woman in the Chamber of Commerce and very much valued." She was married at 19 years of age to a shoe salesman, who is 41 years of age, living and well. One child is living and well. She had no miscarriages. She does not use alcohol. Her sexual habits are normal. Her medical history is negative. She has not had any previous illnesses.

*Present Illness.*—The history is repeated as given by the husband who seemed to be an intelligent and reliable informant. Four or five years ago the patient began to find her work difficult, and she began to lose weight. She was noticed to change in disposition, becoming tired, irritable and easily upset. She was annoyed by trifling things, such as careless dressing of strangers. This tendency increased and six months ago she began to be suspicious of her fellow workers. She said that the other girls talked about her, laughed and looked at her hair and at her clothes. This she put down to the fault of the woman who was at the head of them, who, for some unknown reason, was "down" on her. This woman had been a friend of hers. She also had ideas of reference on the street. All this took place despite the fact that her work was of excellent quality and her wages had been increased.

She took a two weeks vacation in August, at which time she had a bad headache, which lasted a month. She was given medicine and it went away. August 17 she contracted influenza and was in bed for five days. She had a fever but was not delirious. She recovered, but was advised not to return to work until the end of the week of admission. September 25 she was apparently as well as ever, and had taken a walk on the day before. She was not at home in the evening when her husband returned from work. Search for her was in vain. She was not seen until the next day, when she was found in the park on the grass, wet to the skin, with her hair down. She stared at her husband and could give no account of herself. She seemed to be unable to speak. At night she seemed to be trying to tell him something, but could not get it out. She kept saying "yes" repeatedly, and waved her arms as though someone was chasing her. The only coherent sentence she made was that she had brought her hat home anyway. She did not sleep that night, but kept repeating, "I am going to get rest" and rubbing her eyes. She seemed to be totally disoriented for time, place and person.

*Mental Examination.*—The patient, when brought to this hospital, gave a scattered account of herself with mention of the various factors related by her husband in an incoherent, straggling fashion, grimacing as she spoke and showing great emotional dullness. She was approximately oriented at that time. Mental examination was somewhat hampered by her retarded ideation and sluggish thought processes. Her consciousness was not clouded. Her memory was very defective in the characteristic patchy manner. Thus, although she could give correctly simple items of school knowledge, she could give no account of her illness and a very incomplete account of her past life. There were no delusions or hallucinations, nor, on the other hand, any insight. Thought processes showed attention rapidly gained, but retained with difficulty, retarded flow of ideas and slow, incoherent associations. She initiated no conversation. Her emotional tone was distinctly dull and apathetic. Her conduct was quiet and aboulie. She grimaced a great deal, especially accompanying her speech. There was a slight speech defect. Her condition did not change in any respect during her stay here of ten days.

*Physical Examination.*—The patient was a fairly well developed and nourished white female, quiet and cooperative, with an entirely negative physical examination except for mildly hyperactive knee jerks, a doubtful Babinski on both sides, and pupils which were irregular, unequal in that the right was slightly larger than the left, and a reaction as follows: "Both react slowly and through a narrow arc to light, the right one being more sluggish; reaction to accommodation normal." The blood pressure was 100-50.

*Laboratory Findings.*—The urine was negative. Vaginal and urethral smears were negative. The blood Wassermann was positive. Spinal fluid examination showed globulin ++, albumin ++, cells 121 (99 small lymphocytes, 19 large lymphocytes, 3 neutrophilic polymorphonuclears). The gold sol reaction was 5555444430.

*Psychometric Test.*—The patient graded slightly irregularly with a variation total of twelve, at a mental age of 8.8 years. The performance on the construction puzzles was poor, and on the memory tests very poor. In the suggestibility test she accepted six out of ten suggestions. She cooperated well and seemed interested.

*Diagnosis.*—General paresis (neurosyphilis paretica). The patient was committed.

CASE 7.—*Cyclothymia + Alcoholism + Influenza (+ Syphilis) = Paresis.* This was a harlequin case of very unusual features. The patient was a male, aged 61 years. He had had many commitments for cyclothymic and alcoholic psychoses. He was apparently normal for a time, then influenza, and thereafter an acute psychosis disclosed a general paresis. This man was born in

New Brunswick. His parents were born in Ireland. Nothing more than this is known about the family history.

*Past History.*—The patient's past history is largely a record of his successive commitments. Nominally, he was for the most of his life a common laborer in the saw mills and woods of the north; actually he spent much of the time in various state and provincial hospitals.

At the age of 23 he was committed to a provincial hospital in Canada with the conventional diagnosis of "melancholia." Thereafter he was probably committed numerous times, but no records could be secured until his commitment to a state hospital in Maine at the age of 52, because of conduct disorder accompanying agitation and depression. Thereafter he was committed time after time, in each instance with the same symptomatology, and usually the same diagnosis, "Manic depressive insanity, depressed phase, with alcohol as an exciting factor." Alcoholic hallucinations was diagnosed twice. The symptoms would abate in from two to six months, and he was never kept longer than the latter period. He is known to have been committed fourteen times, and the actual number of commitments is probably considerably greater.

"Diminished knee jerks" is the only evidence of nervous pathology offered by the clinical records of the hospitals where he was committed. Apparently laboratory tests were not made.

*Present Illness.*—For eighteen months he had been free from any mental symptoms, having been discharged then from a state hospital with the diagnosis of "alcoholic hallucinosis." (He had been deluded, hallucinated, depressed, retarded and self-accusatory. On a priori reasoning the diagnosis is certainly open to some doubt.) He had been working (and drinking) steadily until three weeks before admission when he contracted influenza. It is not known exactly how long he was ill. He was in the hospital of the Falls River ship building plant. About a week after his discharge therefrom, he began to be talkative in an irrelevant, incoherent and unintelligible manner. Typical of this is his reply to the question in the admission office, "Have you delirium tremens?" which was . . . "It was upset in the bag. I have heard them talking all day." He readily accepted the suggestion that he had been doped, and went willingly (although vociferously) to the ward.

*Mental Examination.*—A routine mental examination was never possible as he was completely inaccessible and uncooperative. He wandered constantly about the ward, jabbering in a monotonous voice an endless rigmarole. His replies were irrelevant, incoherent and meaningless. Attention could be gained for a moment but it was impossible to hold it longer. His ideation and thought content could not be determined, or his memory tested, because of his desultoriness and irrelevancy, but he seemed at times to be correctly oriented for time and place ("state hospital"). His conduct disorder consisted in a multitude of trivialities, uncleanness, denudativeness, removing his clothes and washing them in the hopper, wiping his face with his socks, ruffling the bed, etc. He showed no tendency to violence. His emotional tone was that of a mild euphoria, with a rather general indifference to most of his environment. He was probably constantly hallucinated.

*Physical Examination.*—He was a well developed and well nourished man, rather bald, with no anomalies or malformations. The general physical examination was entirely negative, save for a harsh systolic aortic murmur, with evidence of considerable peripheral arteriosclerosis. The blood pressure was 130-60. The neurologic examination was negative, including the ophthalmoscopic, except for a fine tremor of the hands and diminished knee jerks. Coordination could not be well tested, but seemed poor.

*Laboratory Findings.*—The urine was negative. The blood serum Wassermann was positive. The spinal fluid Wassermann was negative (!). The spinal fluid globulin and albumin were normal (???,KAM); 56 cells. The gold sol reaction was 5544443200.

*Diagnosis.*—The man was committed with the unqualified diagnosis of neurosyphilis paretica (genera paresis). (The staff presumably, and I certainly, agree heartily with Hunt's<sup>16</sup> recent dictum, "The gold test is the one of all most to be relied on.")

One of the interesting facts about this case is the unusual combination of alcoholism, syphilis and cyclothymic psychosis with the precipitation of badly demented paresis by an attack of influenza. A second remarkable thing is the absence of neurologic signs in the presence of so manifestly advanced paresis. A still further remarkable fact, and one which may be contested by a few, is the rather equivocal laboratory findings in the spinal fluid. Not only is it unusual to have normal albumin and normal globulin with general paresis, but the concomitant finding of fifty-one cells makes the examination open to doubt. The gold sol reaction is quite typical. The negative Wassermann, while quite unusual, is not at all without precedent.

NOTE.—At the state hospital to which he was committed he showed quite a different picture within the next few months and developed additional symptoms. The left ankle jerk disappeared, the right became sluggish. A contralateral adductor response was elicited on both sides. Pupils and speech remained normal. Mentally he is described as being defective in orientation and recent memory, dull and apathetic emotionally, and "harboring vague ideas of self accusation, reference and fear." The diagnosis made there (in the absence of serology reports) was split between dementia paralytica, dementia praecox, dementia senilis (arteriosclerotica) and dementia alcoholica.

GROUP 3.—Cases in which the previous symptoms were diagnostic of mental disease (nervous syphilis) but were intensely aggravated (to a committable degree) by the influenza.

CASE 8.—(*Syphilis* +) *Queerness for Several Years* + *Influenza* = *Advanced Paresis*.—A male, aged 40, for some years considered queer, recently became troublesome. He had influenza, followed by visual hallucinations, disorientation, amnesia, etc.

*Family History.*—The patient was one of twenty-two children, of whom all but seven died in infancy or youth. The mother also had several miscarriages. His father had twenty-seven brothers and sisters, and the mother an equally surprising number (exact figures not known). There is no history of mental or nervous disease.

*Past History.*—His childhood was uneventful. He left school to begin work at 14 and worked in shoe factories thereafter. His maximum earnings were \$36 per week. He was married twenty-three years previously to a French Canadian woman. It was not a very happy marriage. He has eight living children. His wife had no miscarriages.

*Present Illness.*—(Paraphrased from the physician's written statement and the history furnished by wife, sister and father). For several years he had been acting queerly at times, such as "talking loudly to himself when alone, asking questions as if talking to other persons and giving the answer himself." Recently he had seemed tired and complained of headaches. Two weeks before Christmas he assaulted his daughter, striking and injuring her. Christmas day the doctor was called and diagnosed influenza. His temperature fell to normal

16. Hunt, E. L.: Some Practical Points in the Diagnosis of Syphilis of the Nervous System, *Med. Rec.* 95:393 (March 8) 1919.

January 2. January 1 the patient had seemed more queer than ever. He reacted to hallucinations for about an hour in the afternoon. This recurred the following day, with a normal temperature, and again thereafter. He would speak of the (imaginary) child he was holding, direct his wife to pull (an imaginary) chain from the ceiling, etc. He began to mistake identities, called his wife by a wrong name, imagined "every day to be Sunday," thought himself in a western Massachusetts town, etc. He also began to be disturbed and unruly at night and finally was brought to the Psychopathic Hospital, "his lucid intervals growing shorter and less frequent."

*Mental Examination.*—He was a dull, apathetic man, aged 40, but appearing older, who answered in a low, indistinct voice without any attempt at cooperation. He was grossly disoriented, especially in the temporal sphere. His memory showed a severe grade of deterioration, there being almost no coherent memory for either recent or remote events. He could not remember when he was born, whether or not he attended school, who was president, etc. Characteristic of his disorder, he recalled and gave correctly some minor but complicated facts such as the list of New England states, etc. While no delusions or hallucinations were elicited, he had absolutely no insight, and did not understand why he was in a hospital except that he "had some diarrhea" or "was dizzy last week." His thought processes showed utter decimation; his attention was fleeting; his associations were loose and weak; his train of thought broken and incoherent. His emotional tone was that of complete indifference. Any expression of emotion that he did give was obviously only verbal. His motor status was in general characterized by inactivity, aboulia, hypokinesia. At times he got up and wandered about the ward, becoming lost, and requiring to be led back to his bed or chair. There was a very slight speech defect, frequently, but not always detectable. Much more prominent was the low, indistinct, disinterested manner of speech, representative of his severe dementia. He did not change in any material way.

*Physical Examination.*—(Summary.) A well developed and nourished man, aged 47. He has no subjective complaints. Smell, vision, hearing, taste, sensation, gait, station, speech and all reflexes are normal. There are no paralyses, clonuses, atypical reflexes, atrophies, vasomotor disturbances, etc. The pupils are equal but irregular; they react through a narrow arc, but promptly, to light. The blood pressure is 130-75. Physical examination is otherwise negative.

*Laboratory Findings.*—The urine is negative. The blood serum Wassermann is positive. The spinal fluid showed globulin ++, albumin ++, 17 cells (15 small and 2 large lymphocytes) and a gold sol reading of 222322000.

*Diagnosis.*—Neurosyphilis (paretica).

**GROUP 4.**—Cases of neurosyphilis in which the clinical manifestations and course were not perceptibly influenced by the influenza.

**CASE 9.**—*Tabes Dorsalis, Arrested, + Cyclothymia + Influenza = Cyclothymic Psychosis (Neurosyphilis Unaffected).*—A male, aged 52, clerk, married, had tabes, the result of syphilitic infection at 18. There was good response to treatment; the symptoms were arrested. He had influenza followed by a typical episode of manic depressive insanity of the depressed phase. The syphilis manifestations were unaltered.

*Family History.*—Negative.

*Past History.*—His childhood was essentially normal. He went to school from the age of 6 until 18, completing two years in a university. For twenty years he has been clerk for a railroad at \$34 a week.

His habits have been regular for many years. He drinks one or two whiskies daily, but is never drunk. In 1892 he married a woman who proved to be alcoholic and immoral. He has been divorced for twenty years. Two children are living and well. His wife states that he was apparently dis-

tinctly subject to melancholia, humors, moods, but without previous psychotic episodes. He had pneumonia thirty-two years previously and contracted gonorrhea and syphilis at the age of 18. Treatment at that time consisted of mercury pills. He was treated at the Peter Bent Brigham Hospital, to which hospital I am indebted for the following abstract:

June 30, 1917. Patient admitted to the hospital. For the last three or four years the patient has been incontinent of urine, has been conscious of a constricting sensation about the waist, and has had irregularity of the size of the pupils. For two years vision has been gradually failing with diplopia in looking at distant objects, unsteadiness of gait and difficulty in walking in the dark. The pupils are unequal, irregular and do not react to light. There is marked impairment of vision of the right eye, there being no vision on the nasal side. The inguinal glands are distinctly enlarged. The knee jerks are absent and the Achilles and plantar reflexes are diminished. The gait is ataxic and the Romberg sign is present. The Wassermann and spinal fluid are positive.

July 20, 1917, the spinal fluid showed forty cells and a globulin  $++$ . He received one intravenous and one intraspinal injection of diarsenol. He has also received intramuscular injections of mercury succinamid. The pupils are fixed; the knee jerks are absent. Discharged. Diagnosis: *Tabes dorsalis*.

Patient was admitted at various intervals, a total of ten, for treatment. His last admission was Sept. 14, 1918. Physical examination at that time showed the right pupil smaller than the left. Both are fixed. The knee jerks are absent. The muscle sense is good. He sways slightly in the Romberg position. The spinal fluid shows eight cells and a slight possible trace of globulin. The Wassermann is  $++$ . Discharged Sept. 15, 1918. Diagnosis: *Syphilis; tabes dorsalis*.

Three months prior to his admission here he reported at the Brigham Hospital and was told that his spinal fluid showed no signs of syphilis. Since that time he had had a second test which was also negative.

*Present Illness.*—Four weeks prior to admission he developed influenza (October 4), and was in bed for several days. He had not felt well since and did not return to work. The night before admission (October 31) he became excited, insisting on telling his relatives about his condition—that he had syphilis and would never get well. He insisted that he was “all in,” in a dreadful condition, that his case was entirely hopeless, etc. He described a great many symptoms which he actually did not have, and had not had for some time, such as urinary incontinence, and insisted that his bowels had not moved for weeks.

*Mental Examination.*—The patient entered expressing ideas as indicated above, but without hallucinations and without any impairment of memory or intellectual processes. This was accompanied by depression and at times apprehension and agitation. His thought processes were retarded, but not greatly, and his motor status was normal. Following the lumbar puncture he was even more depressed. “Thinks that his *tabes* has advanced to such an extent that nothing ever can be done for him.” Later he decided that he was growing much worse, that he was to die very soon, and feared that he might start a pestilence here. He decided he could detect uriferous odor about himself.

*Physical Examination.*—The patient was poorly developed and badly nourished, complained of paresthesias, but showed no evidence of physical disease, except neurologic findings which were as follows: The special senses and sensation were normal; the muscle sense was good. There was no vasomotor disturbance. Moderate atrophy of leg muscles was present and evidence of an old fracture. The ocular movements were normal. There was no ptosis, nystagmus or strabismus. The pupils were dilated, equal and round; reaction to light and distance was absent. The pharyngeal reflex was present. The cremasteric reflex was not obtained. The knee jerks were absent. His gait was unsteady. The Romberg was positive. Coordination was poor. No

Babinski or clonus was present. The periosteal reflex was absent. There was essentially no change in his condition.

*Laboratory Findings.*—The urine was negative. The spinal fluid showed globulin +, albumin +, two cells. A sensitive gold sol reaction read: 0111233430. The Wassermann reaction was positive in the first three dilutions. The serum Wassermann was not reported.

Ophthalmoscopic examination showed an old optic atrophy of the right eye and a normal left fundus, except for a very heavy pigmentation.

November 25, twenty-five days after admission, he was transferred to another state hospital with a diagnosis of depression with tabes. The minority of opinion favored the diagnosis of manic depressive insanity, depressed phase.

I do not regard the neurosyphilitic process as having been manifestly altered. The psychotic episode passes very well for the depressed phase of a cyclothymic psychosis, although depression with tabes is a recognized syndrome which might be defended vigorously. Perhaps it is wrongly classified here, but if so it deserves a class for itself.

*CASE 10.—Congenital Neurosyphilis + Influenza = No Change.* A female, aged 21, with congenital neurosyphilis, had hemiplegia for five years and seizures for two years. Influenza was followed by no alteration in the symptomatology or course.

*Family History.*—Her father died of general paresis. Her mother died in this hospital, probably from bronchopneumonia following influenza. One sister aged 19, is strong and supposedly healthy.

*Past History.*—She was born in Boston and spent an uneventful childhood. She graduated from the grammar school and took stenography and book keeping courses, with good records in both. She was not backward either mentally or physically and was always considered healthy until the present illness.

*Present Illness.*—Five years previously she was first troubled with failing vision, then with some difficulty in moving her fingers and hand (left) and was soon after taken with a complete left hemiplegia. This persisted, although the leg improved and she became able to get about somewhat, but her mother was obliged to do most things for her.

For the past two years, in addition, she has had frequent seizures in which she was unconscious for from fifteen to twenty minutes, falling to the ground, rigid, and afterward amnesic and drowsy. The seizures sometimes occurred twice or thrice a day. At other times she thought she felt quite normal. A year prior to admission she was given some intravenous injections and for five months subsequently did not faint. Three months before admission she seemed to be much better and improved in disposition.

November 27 she was taken ill with influenza. Her mother was taken ill simultaneously and died at this hospital about December 10. The patient was febrile (maximum 102 F.) for at least several days, and was in bed for over a week. She entered the Psychopathic Hospital December 6, chiefly because she was deprived of her caretaker (the mother).

She denied any change in herself since the influenza, and has not had any seizures prior to her admission to this hospital. (She had several here, however).

*Mental Examination.*—This was entirely negative in every way, except that the patient was somewhat restless. She seemed somewhat dull emotionally, which was thought possibly due to her recent illness. She was pleasant and fairly cheerful. She had two convulsions during her week's stay in the hospital, at which time she was unconscious, rigid, twitched, frothed at the mouth, breathed stertorously, but was not cyanosed. She took the death of her mother with considerable weeping, but reacted in a few days.

*Physical Examination.*—She was a rather poorly developed and badly nourished girl, 5 feet, 5 inches tall, weight, 115 pounds, with a left paraplegia. There were no marked asymmetries or anomalies. Smell, taste, hearing, vision, cutaneous and deep sensibilities were normal. There were no abnormal movements of face, tongue or lids. Coordination of the right hand was good; the left hand was paralyzed. The loss of motion in the left leg was less than in the arm. There was some atrophy of the muscles of the eye and left arm, but no vasomotor disturbance. Corneal and pharyngeal reflexes were present. The left abdominal reflex was absent. There was no Babinski nor ankle clonus. The muscles of the left side of the face were weak. All reflexes of the left side were hyperactive. The right side was normal. The left pupil was dilated and did not react. The blood pressure was 108-78. Heart, lungs and abdomen were negative.

*Laboratory Findings.*—The urine was negative, except for the slightest possible trace of albumin, and the presence of bile. The spinal fluid showed globulin +, albumin +, two cells. The gold sol test was 0012321100. The spinal fluid Wassermann was insufficient. The serum Wassermann was not reported.

*Psychometric Examination.*—The patient graded at a slightly irregular mental age of 12.5 on the point scale, and 12 years 10 months on the Stanford scale. She cooperated well.

*Diagnosis.*—Neurosyphilis (vascular type; congenital).

#### ADDENDA TO GROUP IV

Dr. Cohoon, superintendent of the Medfield State Hospital, was kind enough to make a personal investigation of the effect of the influenza epidemic on the neurosyphilitics in his institution, and has furnished his data in a personal communication. Practically all the cases there observed fall into Group 4 of this classification. Of five males, three were unchanged; two died of pneumonia. Of eleven females, two died and nine were unchanged.

This substantiates a generalization which is confirmed by all our data, namely, that the acute infection influenza has an accelerating influence on the incipient cases of neurosyphilis (and in fact on mental disease in general) which often becomes strikingly manifest, but on the advanced cases has generally no demonstrable effect, and certainly not the beneficial influence once looked for.

**GROUP 5.**—Cases of neurosyphilis which were apparently improved following the influenza.

We have observed no such cases, and the investigation at the Medfield State Hospital reports none. Two of the patients at the latter institution were already improving under intensified therapy, but were not perceptibly affected by the influenzal attacks. The literature mentions such cases, but in vague terms with uncertain references, so that it may safely be said that there is at present no evidence that such a fortunate occurrence ever takes place.

In the literature the example of Oeteke (quoted by Klemm<sup>17</sup> without reference) is typical in its vagueness. "In only one paralytic

(general paresis?) in a remission did there occur after influenza with severe pleuropneumonia a considerable and inexplicable improvement in the mental sphere."

Finally, I append two cases which are probably not cases of neurosyphilis. At least such a diagnosis cannot be made positively, although the symptoms of the one case are very typical of general paresis, and the case was so considered until the absolutely contra-indicative laboratory findings were received. When time has finally diagnosticated these cases, if it ever does, the present attitude toward them will be an interesting retrospect.

CASE 11.—*Normality (?) (+ Syphilis?) + Influenza = Mylitis Spinalis (?) Neurosyphilis.* A male, aged 37, after an attack of influenza developed urinary incontinence and sensory disturbance of the legs. The diagnosis was in doubt.

*Family History.*—Negative.

*Past History.*—Essentially negative. The patient had always been well, and he had been efficient economically.

*Present Illness.*—After an attack of influenza, in January, 1918, he developed a sensation of tightness over his chest and abdomen and a numbness of the legs. This began three weeks after the grippe attack terminated. Concomitantly dysuria began, followed by retention. Thereafter, he was catheterized daily and later became incontinent. At this time he was treated in an excellent general hospital. It was noted that the pupils were unequal, but reacted well, and that all reflexes were hyperactive. A lumbar puncture at this time revealed a spinal fluid containing eighty-two cells, positive globulin test, and 2 + positive Wassermann on 1 c.c. of spinal fluid. The blood Wassermann was negative. He was given two intraspinal treatments, both of diarsenolized serum with the diarsenol brand of arsphenamin reinforcements. Thereafter he received more antisyphilitic treatment and was discharged improved after three months.

He continued, however, to have the paresthesias and pains, and with them more or less difficulty with urination, which, together with his neurasthenic disposition, made him an exceedingly unpleasant companion. He was persuaded to go to the Psychopathic Hospital, where he was observed at long periods for the next year, and given considerable anti-syphilitic treatment.

*Mental Examination.*—This was chiefly negative, although he was exceedingly neurotic, complained much and cooperated poorly. There were no definite psychotic symptoms.

*Physical Examination.*—This examination showed remarkably few neurologic signs. All reflexes were hyperactive, but equal, and there were no abnormal reflexes or abnormal neurologic signs. At this time, speech and writing difficulty were thought to be present, but this was not confirmed. The blood pressure was 110-70. Some paresthesias and hyperalgesias were discovered, but nothing marked. Girdle pains were complained of at times; leg pains were also described, and vomiting attacks were sustained.

*Laboratory Findings.*—The twenty-four hours urine specimen was negative, except for a very slight trace of albumin. The blood cytology and blood serology were also negative. The spinal fluid examination showed globulin ++, albumin ++, nine cells, gold sol test 0001342110. The Wassermann test was negative.

*Diagnosis.*—A very excellent general hospital made the diagnosis of tabes dorsalis, but it was not felt here to be justifiable to retain this diagnosis. The opinion of the staff was divided on the basis of the possibilities of a modifica-

tion of the Wassermann reaction by the intraspinal treatment received. Intramedullary tumor, nonsyphilitic myelitis, and neurosyphilis spinalis were suggested as the three most likely possibilities.

*CASE 12.—Mild Premonitory Symptoms + Influenza = Pseudoparesis.* A male, aged 51, Jew, tailor, born in Russia, had resided in Massachusetts for thirty-five years.

*Family History.*—This was negative, except as follows: The paternal grandmother is said to have been insane for a short time (before death?); a paternal uncle "was insane in W—— state hospital. He burst a blood vessel on the brain and died after two weeks," and a paternal (female) cousin was insane for a short time after childbirth, was in T—— state hospital. "She thought she was a princess and that her mother was against her." "The paternal side are all said to be peculiar and to have an odd way of smiling at times when it was more appropriate to cry." (From wife's statement.) Siblings: The patient has two brothers in Russia, one sister in New York and one sister in Texas, "who was said to be insane for a short time."

*Past History.*—He came to the United States at the age of 18. He learned to read and write Hebrew at a night school in this country. He has followed various trades and invested in various businesses, including shoes, cleaning and dyeing, automobiles, tailoring and book making. He made "a comfortable living" while he owned a tailor shop, but the war conditions pushed this out of business, and since then he has been in reduced circumstances. Marital: He was married twenty-seven years previously to our chief informant, now aged 48, who was healthy and fairly happy in her married life. Children: He has a boy, aged 26, a sailor in the U. S. Navy; one boy died of grippe, aged 1 year; a daughter, aged 22, is "nervous and anemic"; a boy aged 20 is in the U. S. Army; a daughter, aged 10, is in the seventh grade. His wife has had two miscarriages, one at three months. Disposition: "He is good natured, though quick tempered, but not abusive. He is very fond of the children and helps a great deal with their care. He is active, fairly sociable, has a good deal of pride, likes to look well, and is generous." He is of the Jewish faith, but takes "no interest" (wife). Habits: He drinks beer, but never to excess. He has a good appetite.

His medical history is negative; however, "six or seven years ago he had headaches from drinking coffee and had to give it up. About seven years ago he was ill and was told by his doctor to have no sexual intercourse with his wife." This he associated with the moral of Brieux's play, "Damaged Goods," which he had just seen, and "was afraid it was something of that nature."

*Present Condition.*—(Where quoted, statements are taken from our historian's history as obtained from the wife.) "For about two months the patient has complained of headaches and of a noise in his ear which sounded like machinery. For about a month he has been forgetful; he would ask his wife to write down any errands he was given to do." He was laid off work on December 17, and on the nineteenth began to look melancholy. He did not complain of anything, however. The next day he went to his wife's place of employment and went to sleep, which was quite extraordinary.

December 21 he was sick in bed with influenza, his temperature reaching 100 F. The whole family had it at the same time. The next day the temperature is said to have been normal. That night, at midnight, he walked into his wife's sickroom, fully dressed, and announced that he was going to work. He looked about for some man who he said had slept there. "His temperature was taken at that time and found to be normal." He slept that night, but the next day looked "dazed and sad." He remarked, "Funny to let an audience fly," which was totally without meaning to his wife. "His body and hands shook." He went to bed but soon arose to attend to the furnace. "He staggered and appeared to lose control of his limbs. He asked for some of his children whom he should have known were away."

He began to lose weight and his breath was noted to be foul. "While in bed and apparently asleep, his eyes being shut, he talked about his work to some one he seemed to think was in bed with him." He has lost his memory for recent events, but for the remote past it remains intact. Early in the morning of December 31 he came into his wife's room, sat on the bed of one of the children, and pulled a blanket over his knees. When told to return to bed he said he was in bed and asleep. His pajamas were off and he had on a bathrobe. His wife found his own bed torn to pieces. He mumbled unintelligibly. He had had no outbursts, delusions, hallucinations (?), ideas of reference, dizziness, convulsions, shocks or fainting spells. He was admitted to this hospital January 31.

*Mental Examination.*—The chief findings were as follows: He was accessible and slightly cooperative. He was quite disoriented temporally, giving the day wrongly, the month as November (it was then December 31) and did not know that Christmas day, which was also his daughter's birthday, had just passed. He showed a distinct impairment of memory for recent events, but not much for remote events. He showed no frank delusions or hallucinations. His thought processes showed distinct retardation and dulling, but there was no gross incoherency or irrelevancy here shown. His emotional tone was rather flat, although there was some euphoria at times and a mild apprehension at others, when he would go about trying all the doors. His motor status was normal save for frequent exhibitions of restlessness, and periods of apparent bewilderment, described in the notes as "confusion."

*Special Tests.*—Speech showed a distinct defect with the conventional test phrases. His writing was also defective, and he wrote in a tremulous scrawl. The spelling is here reproduced:

181 Hann(m)mond St.  
Ca?mbridges  
Common w(ue)alt

Of his calculating ability the following figures made in an attempt to subtract 28 from 1918 are fully expressive:

26  
168  
11788  
11888  
1533

Ophthalmoscopic examination showed nothing abnormal in the left eye, but in the right "a dilatation of the vessels and a loss of distinctness of the nasal half of the optic disc, with evidence of mild inflammation; cup absent. Low grade monolateral optic neuritis."

*Physical Examination (Summary).*—Patient was a well developed and well nourished man. There were no abnormal reflexes. Local tenderness was present along the nerve trunks in the region of the right calf. The pupils were contracted, irregular, and reacted through only a moderate arc, but promptly to light. The blood pressure was 100-60 (? sphygmometer). Coordination was good and neurologic and physical examinations were otherwise negative.

*Laboratory Findings.*—Blood examination: Hemoglobin, 85 per cent.; red blood count, 4,680,000 cells; white blood count, 8,400 cells. The serum Wassermann was negative; the urine was negative and throat cultures were negative. The spinal fluid showed albumin normal; globulin absent; twenty-three cells, of which thirteen were small and five large lymphocytes, and five endothelial cells. The gold sol reaction, first time showed 1112100000; the second time (same fluid) the test was negative. The Wassermann was negative.

He had a constant rectal temperature of 99.8 F. Epinephrin had no constant effect on the blood pressure. He was removed against advice by his wife who refused commitment.

## CONCLUSIONS

The interrelation of coincident infections is studied from the data presented by cases of neurosyphilis affected by attacks of influenza.

Cases are cited to illustrate three effects of influenza on neurosyphilis:

1. The precipitation of profound symptoms in previously latent neurosyphilis by influenza.
2. The augmentation of symptoms and signs of neurosyphilis by influenza.
3. The absence of palpable effect of influenza on the neurosyphilitic process.

The latent, incipient, and early cases of neurosyphilis seem to be susceptible to precipitation or augmentation by the added neurotoxic effects of influenza; the advanced cases are not usually perceptibly altered in symptomatology or course.

No instances of improvement of neurosyphilis following influenza were observed.

The scanty literature is collected and epitomized.

## FEVER AND THE WATER RESERVE OF THE BODY\*

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### INTRODUCTION

During the course of continued intravenous injections of glucose in dogs<sup>1</sup> and man<sup>2</sup> described elsewhere, fever was observed under certain conditions, namely, when the rate of sugar injection was sufficiently in excess of the tolerance limit to produce a marked glycosuria with its concomitant diuresis; when the rate of water administration was less than the rate of diuresis and when these conditions were sustained until the animal or man had lost a certain weight by dehydration. Chills were also observed to occur under the same conditions after the body temperature had begun to rise. Both chills and fever were seen to subside when enough additional water was administered. In the experiments on dogs, the rates of sugar administration were controlled by one motor driven pump, the rates of water injection by another pump. The urine was collected and measured continuously by a catheter retained in the bladder which emptied into a graduated cylinder. The animals lay constantly on the platform of a scales, sensitive to 10 grams. Under these conditions the water balance was subject to absolute control and gains or losses of 10 grams or more in body weight were readily detectable. In this way, fever and chills could be made to come and go at will during the course of a single experiment.

The most obvious explanation was that after a sufficient quantity of water had been abstracted from the body, there was not enough left to sustain the normal processes of cooling by evaporation through the lungs (and the skin in the case of man), and that the animals suffered a true thirst fever produced in an unusual way. The view was also expressed that the actual removal of water from the body might not be essential and that the mere presence of a sufficient quantity of extra

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\* From the Otho S. A. Sprague Memorial Institute Laboratory for Clinical Research, Rush Medical College.

1. Woodyatt, R. T.: Studies in Intermediate Carbohydrate Metabolism. Harvey Lectures, 1915-16, p. 326.

2. Sansum, W. D.: Rapid Reduction of Intraocular Tension in Glaucoma. J. A. M. A. 68: 1885 (June 23), 1917.

sugar in the blood and tissues might serve to bind water in a physico-chemical union which would render it unavailable for evaporation at the normal body temperature.

However, various other explanations could be formulated. It might be held that during the rapid injections of glucose an increased oxidation of sugar contributed to the end result, or that the process disturbed a nervous heat regulating "center" or that the sugar set up changes of one type or another in the cells, with fever as a secondary consequence. As a matter of fact, the literature of sugar and salt fevers, beginning with Finkelstein<sup>3</sup> in 1908, contains discussions of all these possibilities without reaching a common decision. The literature is clear, however, in showing that sugar and salt fevers disappear when enough water is administered resembling in this respect "inanition" fever of the new-born, which as Crandell<sup>4</sup> showed is due to thirst. The later writers on salt fever, Heim and John<sup>5</sup> and Peteri,<sup>6</sup> clearly interpret salt fever as a result of decreased evaporation of water due to the hydropigenous (or edema producing) action of salt (sodium chlorid) in the blood and tissues. Nearly all of the literature on this subject has been contributed by the pediatricians and the fevers in question have usually followed single doses of salt or sugar by the alimentary or subcutaneous route in infants. Although fever following single intravenous injections of sugar in adults<sup>7</sup> had been reported before our own experiments, there was, on the other hand, enough difference between the methods of producing salt and sugar fever as described in the pediatric literature and that which we describe that at first it was not clear that we were dealing with the same phenomenon. Early failure on our part to confirm the production of fever by single subcutaneous, alimentary or intravenous administrations of sugar in adult dogs or man, suggested that we were not. But it was later found that this could be done consistently in dogs if the animals were made sufficiently thirsty beforehand. The uniform success of certain pediatricians in producing salt fever in babies suggests that they also have worked regularly with thirsty animals.

3. Finkelstein, H.: Ueber Alimentäre Intoxikation. *Jahrb. f. Kinderh.* **68**: 693 (Dec.), 1908.

4. Crandell, F.: Inanition Fever. *Arch. Pediat.* **16**: 174 (March), 1899.

5. Heim, P. and John K.: Pyrogene und hydropygene Eigenschaften der Physiologischen Salzlösung. Die Bedeutung und Behandlung Exsiccation. *Arch. f. Kinderh.* **54**: 65, 1910.

6. Peteri, I.: Beiträge zum Pathologischen Wesen und zur Therapie des Transitorischen Fiebers bei Neugeborenen. *Jahr. f. Kinderh.* **80**: 612 (Dec.), 1914.

7. Bingel, A.: Ueber Salz- und Zucker-Fieber. *Arch. f. exper. Path. u. Pharmakol.* **64**: 1, 1910.

Our own experiments appeared to offer a very good method of producing and allaying fever in the laboratory under conditions more susceptible to control than any method heretofore used, and it was thought advisable to test its limits as a method. The experiments herein described were undertaken primarily for that purpose. It was also thought desirable to employ the method to investigate further into the mechanism of this type of fever and chills in the hope that light might be thrown on the mechanism and possibly the rational management of fevers and chills in general, particularly the toxic fevers, such as typhoid, the mechanism of which has not yet been settled. Several points bearing on these questions are elaborated in the discussion. The question presents itself as to whether all ordinary clinical fevers are not due in the last analysis to a deficit of free water in the body.

#### EXPERIMENTS

These were designed to determine:

1. How high the temperature of the body can be driven by the technic in question.
2. Whether or not an increased combustion of glucose is a contributing factor.
3. Whether the fever is due to a primary effect of the sugar on the water of the body or whether it is secondary and dependent in any way on a nervous "center" or nervous heat regulating mechanism.
4. Whether it is necessary actually to remove water from the body or whether molecules of sugar within the body can produce fever by their mere presence.

The experiments show that the body temperature can be driven to remarkable heights by this method. Fevers of 111 F. are readily produced, and in one case the body temperature rose to 125.6 F. Fevers of 111 F. were produced by means of salt (NaCl) and by lactose, showing that the increased combustion of glucose is not a necessary factor, which was the conclusion to be anticipated in view of the fact that diminished heat loss and not increased heat production (or supply) is known to be the determining factor in all fevers, that is to say, a great increase of heat production alone does not cause fever because normally a great excess of heat is disposed of automatically by increased cooling. The experiments show that sugar is capable of causing fever by its mere presence in the body under certain circumstances, but that no quantity of sugar which can easily be introduced will cause fever unless the water reserve of the body is for some reason sufficiently low to begin with. Finally, sugar fever can be

produced in dogs which have been rendered poikilothermic by severing the cervical cord, and therefore these fevers are in no sense dependent on a nervous heat regulating mechanism.

EXPERIMENT 1.—A female bull-terrier, weighing 9.3 kilos, was injected intravenously, with a 36 per cent. glucose solution, at the rate of 15 gms. of glucose per kilogram of body weight per hour, for a period of ninety minutes. During this time the animal received 614 c.c. of the glucose solution (containing 221 gms. of glucose) and passed 1,230 c.c. of urine, containing 68.4 gms. of glucose; a retention of 152.6 gms. The fluid output exceeded the intake by 616 c.c., or 66.2 c.c. per kilo. The temperature (vaginal), which was 102 F. at the beginning of the experiment, increased to 102.5 F. by the end of the first hour. A severe chill began twenty-one minutes later and the dog was covered with a woolen blanket. Nine minutes later violent convulsions began and the temperature was found to be 111.2 F. The convulsions became so violent that it was necessary to stop the injection. The urine ceased to flow and thirteen minutes later the dog died with a temperature of 125.6 F., the highest animal temperature that we have been able to find on record. The rise of temperature after the cessation of diuresis amounted to 14.4 degrees.

A postmortem examination was made immediately after death in the presence of Prof. H. G. Wells. The blood was turbid. The red blood cells were crenated to a marked degree. The heart was uniformly dilated to the limit of the pericardial sac. The kidneys and liver were in a state of "cloudy swelling." (Note that in spite of the loss of 66.2 c.c. of water for each kilogram of body weight, with crenation of the red cells, the parenchymas of the liver and kidneys, though dry to the touch, had the appearance of "cloudy swelling.")

EXPERIMENT 2.—The course of this experiment was similar to that of the above, except that no covering was thrown over the animal at the onset of the chills and the diuresis and temperature rise were not so marked.

The dog, weighing 16.9 kilogram, received a 36 per cent. glucose solution, at the rate of 15 gm. per kilogram per hour, for ninety minutes. During this time the fluid intake was 1,029 c.c. and the urinary output 1,470 c.c., a dehydration of 441 c.c. or 27.8 c.c. per kilogram. The temperature, which was 100.4 F. at the beginning of the experiment, rose to 109.4 F.

In previous experiments with glucose injections at the rate of 3.6 gm. per kilogram per hour it was shown that only about 0.6 gm. per kilogram is actually burned. However, the amount of combustion might increase somewhat with the higher rate of injection. Accordingly, increased combustion of glucose might be advanced as an explanation of the abnormally high temperature. We have never been able to give glucose at the rate of 15 gm. per kilogram per hour and maintain the water balance, because the heart is not capable of propelling the necessary volume of fluid. Consequently, we have not been able to determine the rate at which glucose actually burns under these conditions. But we have given 10 gm. per kilogram per hour for a period of seven hours, maintaining the water balance, without the advent of a rise of temperature. (The injection of glucose at rates above 2 gm. per kilogram per hour, will be discussed in a paper on "Intravenous Injections of Glucose at Higher Rates," now being prepared.)

We also performed two experiments, dehydrating with hypertonic sodium chlorid-sodium carbonate solutions, to ascertain how high a temperature might be obtained by employing crystalloids which do not burn in the body.

EXPERIMENT 3.—A female bull-terrier, weighing 10.4 kilograms, was given intravenously 753 c.c. of a 1.4 per cent. sodium chlorid—1 per cent. sodium carbonate solution, over a period of three hours. During this period the dog passed only 255 c.c. of urine. There was, therefore, no absolute dehydration. The temperature, which was 102.2 F. per vagina at the beginning, did not change. The concentration of sodium chlorid was therefore raised to 5 per cent. During the next two hours and thirty-five minutes the dog received 800 c.c. of this new solution and passed 1,875 c.c. of urine. During the course of the five hours and thirty-five minutes of the total injection, the dog received 1,553 c.c. of fluid and passed 2,130 c.c. of urine, a net output over intake of 577 c.c. or 55.5 c.c. per kilogram. Convulsions began and the injection was stopped thirty minutes before death. The temperature rose from 102.2 F. to 113 F. A rise of 9 degrees occurred after the cessation of urinary flow.

Excessive muscular activity during the convulsions might be suggested as a cause of the high temperature. To eliminate this factor a similar experiment was planned and the animal fully narcotized with ether at the first signs of chill, thus preventing the advent of convulsions.

EXPERIMENT 4.—A dog, weighing 10.4 kilograms, received, for a period of three hours, 718 c.c. of a 5 per cent. sodium chlorid—1 per cent sodium carbonate solution, and passed 1,005 c.c. of urine. The fluid output exceeded the intake by 287 c.c. or 28.2 c.c. per kilogram. The first slight twitchings due to a beginning chill began thirty-eight minutes before the close and were immediately stopped by the anesthetic. The temperature rose from 101.3 F. to 111.2 F.

*Fever in Poikilothermic Dogs.*—In order to determine whether the temperature changes during these experiments were in any way grossly influenced by a nervous mechanism, several dogs were rendered poikilothermic by sectioning their spinal cords between the sixth and seventh cervical segments. These dogs were also observed for manifestations of chills. Several experiments were made before the results were satisfactory. Following section of the cord, the body temperature adjusts itself to that of the environment and, at ordinary room temperature, it falls steadily and only becomes constant again at a deeply subnormal level. Under such conditions glucose injections may fail to start diuresis. If diuresis does occur, and it is possible to dehydrate in the usual way, the body temperature may rise materially and still the final temperature may remain markedly subnormal so that one could not then speak of having produced fever in the absolute sense. Again, if the attempt is made to keep the body temperature from falling too low by means of heating appliances, there is danger that fever may be pro-

duced accidentally by the external heat, and it requires elaborate equipment to maintain an operating room constantly at the desired temperature. The simplest method, and one that proved entirely practical, was simply to swathe the animal in cotton or blankets immediately after the operation. In this way the temperature may be kept constant for hours at a level only slightly below the normal.

EXPERIMENT 5.—The spinal cord was sectioned as described above. During the next four hours the dog cooled, spontaneously, to 83.3 F. It was then taken to a room heated approximately to this temperature, 84.4 F. During the next three hours, the dog, weighing 11.5 kilograms, received intravenously 582 c.c. of a 70 per cent. glucose solution, and passed 765 c.c. of urine. The fluid output exceeded the intake by 183 c.c. or 15.9 c.c. per kilogram. The temperature rose from 83.3 F. to 93.2 F., a rise of 9.9 degrees. Slight twitchings of the muscles of the neck and face began just before the death of the animal. Otherwise the usual outward manifestations of chill were missing.

EXPERIMENT 6.—An attempt at dehydration, in an animal whose temperature had been allowed to fall to 77 F., failed on account of the lack of diuresis. An increase in temperature of only 1.8 degree was noted.

EXPERIMENT 7.—In this experiment the cord was severed as before. A covering was placed over the animal to prevent too great loss of heat. In the course of three and one-half hours from the time of the operation, the temperature gradually fell to 95 F., where it remained constant for four hours. During the next four hours the dog received intravenously 752 c.c. of a 61 per cent. glucose solution and passed 1,640 c.c. of urine. The fluid output exceeded the fluid intake by 888 c.c. or 71 c.c. per kilogram. The temperature rose from 95 F. to 106.7 F., an increase of 11.7 degrees. There were no external manifestations of chill and no convulsions.

These experiments prove that the fevers in question are not dependant on a nervous mechanism.

#### DISCUSSION

*General Principles.*—Because of its high specific heat, water is capable of absorbing large quantities of heat, thus preventing sudden high temperature rises in the cells.<sup>8, 9, 10, 11</sup> (It is a noteworthy fact that those tissues in which most heat is produced contain the highest percentage of body water.) Having absorbed heat from its sources of production, water, because of its fluid nature, is capable of distributing the heat equally throughout the body and carrying the excess to the surface where it may be given off. Water then acts as a buffer in high temperature changes, and as a vehicle of heat within the animal body.

8. Mathews, A. P.: Textbook of Physiological Chemistry, New York, 1916.

9. Henderson, L.: The Fitness of the Environment, New York, 1910, p. 80.

10. Stewart, G. N.: Manual of Physiology, New York, 1914.

11. Hunt, E. H.: Regulation of Body Temperature in Extremes of Dry Heat. *J. Hygiene* 12: 479, 1912.

Rubner,<sup>12</sup> Wolpert<sup>13</sup> and Zuntz<sup>14</sup> have established that, in a normal body, as heat production increases, heat elimination by radiation, conduction and evaporation also increase, but that the percentage of heat dissipation by evaporation continually increases as more heat is produced. In other words, normally the loss of heat through evaporation fully compensates for that which cannot take place through radiation and conduction in order to preserve the normal temperature. In fever, however, this is not true. Krehl and Matthes<sup>15</sup> found that during fever, although there was usually an increase of heat elimination by radiation and conduction as well as by evaporation, the loss by evaporation was not sufficient to maintain a temperature equilibrium as in a healthy body. This failure of evaporation to compensate for the loss of heat which cannot take place through radiation and conduction would indicate that something hinders the evaporation of water in fever. Either the total supply of water runs out or the water becomes more firmly bound in the tissues and less available for evaporation.

Further investigations show that when the compensatory loss of heat by evaporation is hindered, hyperthermia results. This has been demonstrated by Sutton<sup>16</sup> who subjected human beings to high temperatures in an atmosphere which contained enough moisture to prevent evaporation. Similar results were observed by Haldane<sup>17</sup> in miners working in warm, damp mines. That most fevers are caused by increased atmospheric temperature, and moisture is of course out of the question. This is true only in cases of sunstroke, heat prostration or the like.

How then may evaporation of body water be checked in other ways? One method of accomplishing this purpose lies in the actual removal of water from the body to the extent that not enough remains to carry off the excess heat. Theoretically, if all the water should be removed from the body the specific heat of all the tissues would be reduced, and with no means left of quickly conveying it to the surface heat would accumulate in the tissues of the body and a high pyrexia

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12. Rubner, M.: Die Beziehungen der Atmosphärischen Feuchtigkeit zur Wasserdampfabgabe. *Arch. f. Hyg.*, 1890.

13. Wolpert, H.: Ueber den Einfluss der Lufttemperatur auf die im Zustand anstrengenden Körperlicher Arbeit ausgeschiedenen mengen Kohlensäure und Wasserdampf beim Menschen. *Arch. f. Hyg.* **26**: 32, 1896.

14. Zuntz, N.: Ueber die Wärme Regulierung bei Muskelarbeit. *Berl. klin. Wchnschr.* **33**: 709 (Aug.), 1896.

15. Krehl, L. and Matthes, M.: Wie entsteht die Temperatursteigerung des fiebernden Organismus. *Arch. exper. Path. u. Pharmakol.* **38**: 284, 1896.

16. Sutton, H.: The Influence of High Temperature on the Human Body, Especially with regard to Heat Stroke. *Path. and Bacteriol.* **13**: 62, 1908.

17. Haldane, J. S.: The Influence of High Air Temperature. *J. Hygiene* **5**: 494, 1905.

would result. This, of course, practically is an impossibility, for a certain amount of water must be present in order that chemical reactions may take place, but less extreme water deprivations, as confirmed by clinical and experimental evidence, inevitably lead to hyperthermias of various degrees.

The researches of Hunt<sup>11</sup> on the effects of prolonged perspiration indicate that there is a large reserve of water in the body tissues which is called out in emergency. Though a large amount of water may be lost without any change in temperature, this investigator believed as a result of his work, that exhaustion of the reserve water would have the same effect as prevention of evaporation by increased atmospheric moisture. So far as we are aware, he did not subject this view to direct experimental test. The present experiments do exactly this thing, and the results are in complete harmony with Hunt's conception.

*Sugar Fever; Salt Fever.*—This brings us to the discussion of sugar and salt fevers as described by the pediatricians. In 1899, Floyd Crandell<sup>4</sup> in an article on inanition fever credits McLane of New York with having first described the phenomenon of fever which develops in the new-born prior to the establishment of the regular flow of breast milk and subsides thereafter. McLane called it inanition fever, believing that the solids of the milk were what allayed it, but Crandell showed that water alone was equally effective, and that the condition was not due to inanition, but to thirst. Similar observations were made by Erich Mueller<sup>18</sup> concerning a form of fever which Halberstadt saw in infants undergoing changes of diet. In 1906, Schaps<sup>19</sup> reported that subcutaneous injections of small quantities of isotonic sugar or salt solution caused fever in normal infants reaching a crest in 8 to 10 hours to disappear within 24 hours. He reported that repetitions of the dose gave weaker results.

We have not seen anything comparable to what Schaps describes and mention it merely in passing as a type of sugar or salt fever which, if it occurs at all, is something different from that which we are here discussing,<sup>20</sup> but in 1908-9 Finkelstein<sup>3</sup> described fever after feedings of 100 c.c. of 12.5 per cent. lactose solution to infants with intestinal disorders. Other sugars and also salts produced the same results. Finkelstein's solutions were strongly hypertonic, his doses were large and his results have been amply confirmed. He made the

18. Mueller, E.: Durstfieber bei Säuglingen. Berl. klin. Wehnschr. **47**: 673, 1910.

19. Schaps, L.: Salz und Zucker Injektion beim Säugling. Gesellsch. f. Kinderh. **23**: 153, 1906.

20. The febrile reactions observed by Schaps and others with isotonic salt solutions have since come to be considered as due to the use of water which was not freshly distilled.

observation most significant in the present discussion, that these fevers could be made to disappear entirely by the administration of tea and even water alone. Thus, Finkelstein saw another kind of fever in infants which, like those described by McLane and Halberstadt, yield under water administration. However, Finkelstein was not clear as to the mechanism of his sugar and salt fevers, and ventured the opinion that they arose from "injuries to cells" caused by the physico-chemical effects of the sugar or salt. Finkelstein thought the cells were injured by physicochemical effects of the sugar or salt rather than by chemical effects, and that much is important. Following Finkelstein a number of communications on the same subject appeared which confirmed the facts but confused more than they clarified the question of mechanism, except the writings of Heim and John,<sup>5</sup> and of Peteri.<sup>6</sup> In summing up the literature in the light of his own observation, Peteri, in 1914, concluded that infection played no part, that external conditions of the atmosphere had been excluded, that the immediate causative factor is desiccation and that the height of the fever attained is in inverse ratio to the body weight. All of these conclusions are in perfect accord with our own reading of the literature, and the results of the present experiments bring proof of their correctness.

Heim and John concurred with Finkelstein's observation that sugars and salts operate to produce fever by their physicochemical effects, which is obvious, for when fever is produced by intravenous injections of lactose, every gram of the lactose given is recoverable unchanged in the urine. The lactose molecule has not been altered. It has done its work as a molecule. But Heim and John went further. Instead of saying that the sugar or salt acted in some unknown physicochemical way on the cells causing the cells in some other unknown way to produce fever, thus begging the question, they suggested that the molecule (of salt) enters the cell and increases the affinity of the cell for water and that it does it in this way. Salt molecules have an affinity for water, and if several hundred of them migrate into a cell, the cell containing them becomes endowed with an increased affinity for water just because it has more salt in it.

This is the conception which Hofmeister first expressed in explanation of the power of a salt in suitable concentration to increase the swelling of colloid jellies. Thus salt in the body holds water in the body by its "hydropigenous" (or edema producing) tendency. As a result, the elimination of water through the lungs and skin falls, cooling is retarded and the body becomes overheated by the continuance of its own metabolic fires. And, it may be added, that as the body warms up more and more, the metabolism becomes faster and faster; a vicious circle is established.

It is unnecessary in this place to delve further into the nature of the affinity of molecules of salt or sugar for water, or to discuss theories of the character of the physico chemical unions of salts or sugars and water in general. It is enough that salts and sugars generally do tend to hold water in association with themselves, and that these substances when added to a beaker of water increase its boiling point and retard its evaporation at any given temperature and pressure. The same may occur in the body. As previously pointed out, the work of the pediatricians with salt fever has been conducted on infants which were in all probability considerably dehydrated to begin with, for as Peteri noted, the heights of the fevers resulting from sugar or salt administrations appear to be related in inverse ratio to the body weight, while fluctuations of body weight are determined largely by the water balance. Moreover, water stops the fever. Our own experiments demonstrate sharply that single large injections of sugar do not, as a rule, cause fever unless the animal is first depleted in water. Therefore, it seems clear that Hunt is right — that there is normally a reserve of water in the body; that a certain fraction of this may become bound by sugars or salts added to the body, but that this binding of water will not ordinarily exhaust the whole free water reserve and determine fever unless the water reserve has been depleted beforehand by actual removal of water from the body as by continued elimination through the lungs, skin, urine or bowels without replacement.

We believe that the discussion up to this point shows that "inani-tion" fever of infants, the fever seen by Halberstadt in infants during alterations of diet, sugar and salt fever in infants, in adults and in animals, are all thirst fevers due to a retarded evaporation of water caused by exhaustion of the body reserve of water available for evaporation at the normal body temperature. One cannot help asking the question: How many more of the fevers which we know in the clinic can also be drawn into the same category?

#### A PHYSICO-CHEMICAL THEORY OF FEVER

We have entertained the following proposition:

Fever, *the symptom* as seen in typhoid, malaria, pneumonia, tuberculosis, rheumatism, measles, serum reactions, proteose intoxication and all ordinary febrile diseases, except insolation and the like, may mean a deficit of "free" water in the body. By the term "free" water we would convey the idea of water in states comparable to those of liquid water at from 20 to 40 C. and ordinary pressures. As A. P. Mathews points out in his book on Physiological Chemistry, 1915, pp. 190-191, the works of Eötvös, Ramsay and Shields and Armstrong, show that

in liquid water at from 20 to 40 C. there probably exist several kinds of molecules ranging in formula from  $(\text{H}_2\text{O})_2$  to  $(\text{H}_2\text{O})_4$ . But in any case, in the present connection "free" water is used to suggest liquid water, capable of absorbing excess heat from the cells, conveying it via the blood to the surfaces of the body and there dissipating it by evaporation, all at the normal body temperature.

Over against "free" water the body contains "bound" water. By this term is meant water molecules associated in the form of hydrates with molecules of other substances such as salts, sugar, protein, etc.; also, of course, water in true chemical combination, but especially the hydration water in colloids. This would correspond to the water reserve of Hunt. It is assumed that the "free" water tends to be in equilibrium with the "bound" water, and that there is a tendency toward the maintenance of a certain "free" water concentration in the blood more or less analogous to the hydrogen ion concentration of the blood, or the blood sugar concentration. When a certain quantity of "free" water is eliminated from the body, its place is filled by more water liberated from the hydrate reserves, and when an excess of free water is taken into the body it is stored as hydrate water or eliminated from the body.

As the colloids are extremely sensitive and prone to change in their capacity to hold water in response to the subtlest chemical and physicochemical influences, it is easy to conceive how the maintenance of a uniform "free" water concentration in the blood might be susceptible to a certain degree of vasomotor nervous control. Thus, the vasomotor nerves, by constricting blood vessels in the liver and causing a relative asphyxia in the liver may increase the production of acid in that organ and so liberate more free glucose from its storage form—glycogen. In an analogous way vasomotor nerves might cause colloids to take up or release more water by causing changes of cell metabolism through variations in the blood supply as needs arose. But the same thing could be accomplished directly by physicochemical and chemical agencies without the assistance of nerves, and nerves could not regulate temperature unless there were free water and responsive cells for the nerves to influence.<sup>21</sup>

It is proposed that in the ordinary febrile diseases, such as typhoid, tuberculosis and others, the symptom fever is due to a deficit of "free" water resulting from an abnormal tendency on the part of the colloids of the body to bind water. The poison of the disease leads to changes of the cell colloids and increases their hydration capacities, so that they

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21. The reader will note that we are discussing fever and the means of the body to prevent hyperthermia or excess of heat; we are not discussing other phases of the problem of regulation of the body temperature.

tend to take up and bind more water. The effect of this on the "free" water of the body is thus the same as that of thirst or the introduction of salt or sugar into the body from without.

It would follow from the above that if we measured the "free" water of the blood in fever, it would be found low even if the total water content of the body were high. It is known that the blood as a whole does commonly become concentrated in fever, but as yet we have no ready method of measuring the "free" water fraction, although means by which this might be accomplished suggest themselves. It would also follow that the cells should be found swollen, the secretions concentrated, etc., which, of course, is the general rule in fever (cloudy swelling of the parenchymatous organs). The thirst during fever and the sudden release of water in the form of urine and perspiration when fever ends by crisis point directly to an abnormal binding of water during the period of elevated temperature. Everyone is familiar with the remarkable emptying out of water via the kidneys and skin which may follow the crisis in a case of pneumonia. Liters of water may thus be liberated in a few hours, giving visible proof of the water retention of the febrile stage. Finally it would follow that if enough water were introduced into the body during fever to saturate the increased affinities of the colloids and provide an excess of free water, then fever should disappear entirely. Now it is possible by copious water administration to lower high grade fevers and to make low grade fevers disappear. The value of plenty of water in fever, and especially in the management of tuberculosis, is too well recognized to require discussion, but probably no one has yet daringly pushed the administration of water in fever to the ultimate limits which might be necessary to ascertain whether every fever can be made to disappear entirely if enough water is given.

The question as to whether it would be good for every patient who presents the symptom fever to eliminate this symptom by means of copious water administration if that were possible, is a question that has been raised repeatedly by friends to whom the present views have been presented. We may be pardoned, therefore, if we emphasize the fact that this question is not under discussion in the present paper. The first objective is to determine whether the symptom fever can or cannot be controlled in this way in a large percentage of cases, and the wisdom of doing so if possible would then remain to be determined by sufficiently numerous experiments in various special types of cases. It is quite conceivable that in some cases the tissues might be so badly poisoned that they would partially liquefy if sufficient water were supplied, and still leave no "free" water available for evaporation at 37 C. The administration of water might then be pushed until mas-

sive edemas or general anasarca supervened before a reserve of free water could be established, or it might prove impracticable to accomplish the desired result at all. These are questions to be answered by experiments.

Up to the present time we have conducted three experiments in pneumonia patients in all of which the body temperature returned to normal within twenty-four hours with the administration of eight liters or less of water. Several observations on diphtheria cases were indecisive, fever persisting in one case after the administration of ten liters of water. A dog poisoned with diphtheria toxin, on the other hand, ran a persistent temperature between 104 and 105 F., until given a large intravenous injection of 3 per cent. glucose solution, during which the temperature fell to normal within five hours. Other work is in progress. So far the results are considered as indecisive.

In closing, attention is invited to the recent work of Lillian Moore,<sup>22</sup> who repeats the experiments which have formed the entire basis for the conception that there are nervous "heat centers" in the brain which, when stimulated, may cause fever.<sup>23</sup> Her results were negative and she draws attention to the absence of any sound experimental support for the current teaching that ordinary fevers are due to derangements of any demonstrable nervous mechanism. She points to the need for a physicochemical theory of fever. The theory outlined above may, therefore, serve to fill a gap. It has at least the advantage that all of the factors which enter into it are concrete things that may be subjected to measurements, and it should be capable of sharp proof or disproof by well designed experiments without recourse to opinion. Whatever the outcome of such experiments, they will, perhaps, add something to our knowledge of the problem.

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22. Moore, Lillian: Normal Temperature Variations and the Temperature Effects of Operative Procedures. *Am. J. Physiol.* **60**:24, 1918. Relation of the Corpus Striatum to the Regulation of Body Temperature. *Am. J. Physiol.* **46**: 253, 1918.

23. The Regulation of body Temperature. *Ed. J. A. M. A.* **71**:1139 (Oct.), 1918.

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# Archives of Internal Medicine

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## IMMUNITY OF CITY-BRED RECRUITS \*

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### 1. THE DATA

#### I. CONDITIONS UNDER WHICH DATA WERE OBTAINED

The presence in our country, during the last four months of 1917, of bodies of men mobilized in army camps gave an opportunity to observe the development of epidemics in crowded communities. The conditions afforded for such study were unusual in all respects, and will probably not be met again for a long time. In the first place, the population of the respective camps came, for the most part, from definitely known areas; so that something could be said about the nature of the population, whether prevalingly rural or urban, and whether from southern states or northern. Indeed, for the most part it could be stated what state or group of states was tributary to a particular camp. In the second place, the entire population was daily inspected and every inducement offered for those suffering from any ailment to go on sick report. Moreover, all cases of admission to sick report were recorded by medical officers and the records sent to the office of the Surgeon-General in Washington, where all records were assorted and treated statistically. A preliminary account of the results gained from the analysis of such reports was printed in a report of the Surgeon-General of 1917. The statistics of 1918 will appear toward the end of the present year in the annual report of the Surgeon-General. However, it appears worth while to lay emphasis on and to develop somewhat more extensively certain conclusions that flow from an examination of the medical statistics of the military camps and cantonments for 1917.

The population of the camps was fairly homogeneous, consisting of men aged from 21 to 30 years, taken direct from civil life, and placed either in barracks (where they slept in beds that were only about six feet apart), or in tents where they were often given an

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\* Prepared in the Section of Medical Records, Medical Department, U. S. Army, and published by permission of the Surgeon-General.

average of less than 50 square feet of space. For men who came from cities, with their crowded factories, offices and shops, this necessary economy of space per man was not novel; but many men from rural districts had never before lived and moved in the midst of such large masses of men. At any rate, the difference in reaction to disease of men from rural and urban districts was striking.

In this paper it is proposed to consider the relative incidence of measles, mumps, lobar pneumonia, cerebrospinal meningitis and scarlet fever and also brief reference will be made to influenza in the camps during the fall of 1917 and the winter of 1917-18. Next will be considered the incidence of these diseases, taken together, in various camps. And, finally, the probable cause of the diversity in incidence of these various diseases in the different camps will be treated. We shall take up, first, then, the six principal epidemic diseases.

## II. DETAILS OF DATA FOR SIX COMMUNICABLE DISEASES

(a) *Measles*.—Measles has always been a great camp scourge, and it was, therefore, in accordance with expectation that a great epidemic of measles affected our army camps in the winter of 1917-18. This epidemic began for some of the camps in October, for others in December, and persisted to January for some and to February and March for others. Before the first of January there had been more than 47,000 cases of measles among the enlisted men in the United States. As stated, the incidence of measles varied greatly in the different camps. This ranged in 1917 all the way from a mean annual admission rate of 500 per 1,000 at Camp Wheeler, Ga., to about one at Camp Wadsworth, S. C. The climatic and housing conditions at these two National Guard camps, located about only 100 miles apart, were very similar. Measles was present at both camps. The tremendous difference in the history of the epidemic seems clearly to be due to a difference in the constitution of the population. The soldiers at Camp Wadsworth were seasoned National Guard troops from New York City and vicinity. The soldiers at Camp Wheeler were mainly newly inducted National Guard troops from Alabama, Florida and part of Virginia, sparsely settled states.

The returns of admission to sick report give the nativity of the patients. It is therefore possible to indicate on a map the number of patients having measles in any camp that were born in each of the states. However, this figure would not have great significance in view of the great variation in the number of native-born sons contributed by the various states. We may supply the deficiency roughly by making the assumption that the number of men in the army born in any state is proportional to the present number of males, age from 20 to 30, in the present population of the state. This assumption has

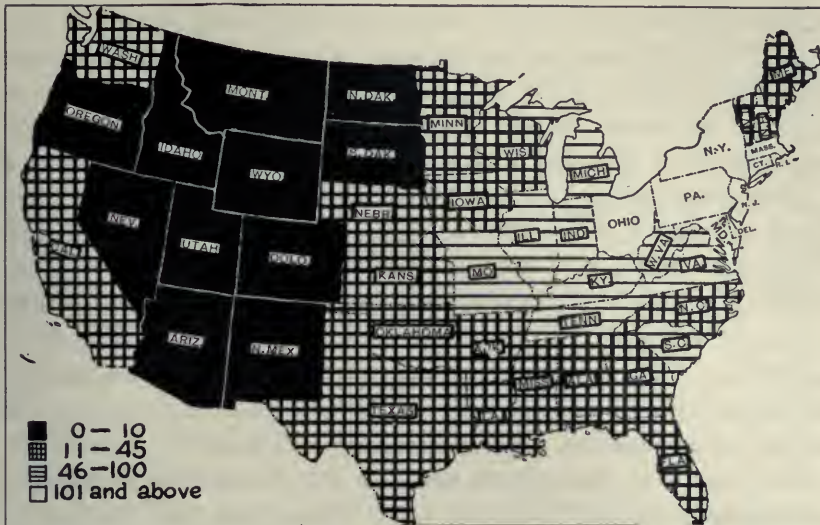


Fig. 1.—Map of the United States indicating relative density of the different states in four grades. The legend indicates the number of inhabitants per square mile. The lighter areas represent the regions of greater density of population; the darker areas, of least density.

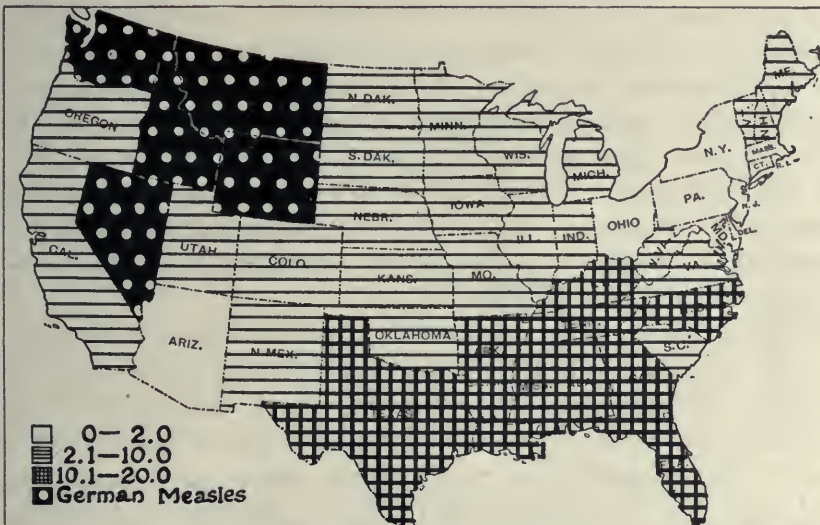


Fig. 2.—Map of the United States showing distribution of admission to sick report for measles by states of nativity of enlisted men, rate per 100,000 of the adult male civil population of each state, age from 20 to 29 years, census of 1910. In three grades. The darker areas represent greater incidence of the disease.

certain large errors, particularly in those western states that have developed rapidly in the past twenty years; but, owing to the fact that there is internal evidence that the state of origin has sometimes been recorded in place of native state, it seems, perhaps, over refinement to make the correction. A map of distribution of measles by native state has been drawn following the suggested method (Fig. 2). In Figure 1 is given a map showing the distribution of the population of the United States by states in four different grades. The comparison of the map of measles with map of density of population shows points of close similarity. Thus, the southern New England States and the Middle States, including Maryland and the State of Ohio, are those of dense population. They are also states with the lowest incidence of measles. The southern Atlantic and Gulf States are those of relatively low density of population. South Carolina has, however, a relatively denser population than North Carolina and Georgia. The table of distribution of measles shows the South Atlantic and Gulf States to be states of high incidence of measles in camps, but South Carolina has relatively less measles than North Carolina and Georgia. There was relatively little true measles in the last three months of 1917 at Camp Lewis, despite the fact that it draws men from a sparsely settled territory. In place of true measles there was a striking epidemic of German measles at Camp Lewis, and the nativity of sufferers from this disease at that camp is indicated by the black area in the northwest section of the map of measles. It may be added that after the subsidence of the epidemic of German measles there occurred early in 1918 a medium sized epidemic of ordinary measles at Camp Lewis.

The close relation between the density of the population and the immunity from measles is the strongest argument for attributing the immunity of measles in camps to the antecedent immunization by exposure to measles in early life.

That persons coming from densely populated areas are more apt to have had measles than those from rural districts is shown by the census of mortality statistics. According to these statistics, in densely populated states like Rhode Island and Connecticut, deaths (and it may be properly inferred cases of sickness) from measles occur at an early age. On the other hand, in rural states like Kansas, Kentucky, Maine and Virginia, deaths occur relatively later in life. This relation between the ages of deaths from measles in urban and rural states is well brought out in Table 1.

TABLE 1.—COMPARATIVE DISTRIBUTIONS OF DEATHS FROM MEASLES BY AGE GROUPS IN URBAN AND RURAL STATES, "MORTALITY STATISTICS," 1915

Urban States	Total Deaths, Measles	Under 1 Year	1 Year	2 Years	3 Years	4 Years	5 to 9 Years	10 to 19 Years	20 to 29 Years	30 to 39 Years	40 to 49 Years	50 to 59 Years	60 to 69 Years	70 to 79 Years	Per Cent. of Deaths Over 10 Years
Rhode Island....	60	19	21	12	3	1	3	.....	.....	.....	.....	.....	.....	.....	0.0
Connecticut....	61	16	26	7	3	2	3	2	1	1	.....	.....	.....	.....	6.7
Rural States															
Kansas.....	73	17	12	10	5	8	6	4	2	2	2	2	1	1	20.6
Kentucky.....	85	18	19	11	2	5	5	9	6	2	1	5	2	.....	29.4
Maine.....	18	2	7	2	1	1	3	.....	.....	.....	1	.....	.....	1	11.1
Virginia.....	58	10	6	13	2	3	5	11	4	1	.....	2	1	.....	32.7

Again, if the states of the registration area of the United States be arranged in rank in respect to the amount of urban population (Table 2), it appears that the proportion of all deaths that are due to measles diminishes on the whole as the percentage of urban population does, while the average age at death from measles increases on the whole inversely with the percentage of rural population. Of course,

TABLE 2.—MEASLES, CIVIL LIFE, PROPORTION OF EACH STATE THAT IS URBAN OR RURAL IN RELATION TO INCIDENCE OF DEATHS FROM MEASLES AND AVERAGE AGE AT DEATH FROM MEASLES, MORTALITY STATISTICS, 1915. U. S. CENSUS

Rank of States in Urban Population	Percentage Urban	Measles per Cent. of All Deaths	Average Age at Death from Measles
1. Rhode Island.....	812	0.673	2.53
2. Massachusetts.....	782	0.511	3.15
3. New York.....	763	0.604	3.04
4. New Jersey.....	650	0.565	2.44
5. Connecticut.....	688	0.334	3.20
6. California.....	429	0.398	6.42
7. Ohio.....	465	0.331	4.94
8. Pennsylvania.....	480	0.491	2.45
9. Maryland.....	477	0.150	4.12
10. Michigan.....	398	0.257	3.85
11. Colorado.....	624	0.198	3.71
12. Missouri.....	370	0.378	7.78
13. Wisconsin.....	343	0.199	4.48
14. Minnesota.....	334	0.382	5.61
15. Indiana.....	330	0.195	6.68
16. Maine.....	231	0.150	9.20
17. Virginia.....	308	0.189	9.95
18. Kansas.....	196	0.401	9.62
19. Kentucky.....	181	0.341	11.00

there are fluctuations on the series, as for example, California; but this is a state of great cities and also great farming areas. So, also, Missouri, while prevailingly rural, is elevated to an unduly high place in the scale of urbanity owing to the two great cities that lie on its borders; consequently, it has an unduly high average of death from measles, though a fairly high proportion of the deaths of the state are due to measles.

Again, the relation between density of population and immunity from measles may be shown by applying the mathematical theory of chance and by calculating the correlation between the proportion of men in the army born in any state who were admitted to sick report for measles, on the one hand, and the urbanity of their respective native states on the other hand. The correlation between these two conditions was calculated from Table 2, and the figure of correlation found to be —80 per cent., a high correlation as correlations go, but inverse (as the minus sign signifies), meaning that the more urban the native state the less susceptible to measles its native born sons in the army (Table 3).

TABLE 3.—CORRELATION BETWEEN ADMISSION RATE BY STATE OF NATIVITY AND PERCENTAGE OF URBANITY OF THE STATE

Per Cent. of Urbanity of State	Measles: Total Admission Rate by State of Nativity					Deviation	Frequency
	0 to 4.9	5 to 9.9	10 to 14.9	15 to 19.9	20 to 24.9		
10 to 19.9	1	4	1	3	2	—30	11
20 to 29.9	1	3	3	1	2	—20	10
30 to 39.9	1	2	..	..	1	—10	4
40 to 49.9	1	6	2	..	..	0	9
50 to 59.9	2	4	..	..	..	10	6
60 to 69.9	1	2	..	..	..	20	3
70 to 79.9	2	..	..	..	..	30	2
80 to 89.9	1	..	..	..	..	40	1
90 to 99.9	3	..	..	..	..	50	3
Frequency.....	13	21	6	4	5	..	49

(b) *Mumps*.—Mumps is one of the commonest infectious diseases in army camps. During 1917 it made up 4.4 per cent. of the total admissions to sick report in the United States, and 11.0 per cent. in Europe.

TABLE 4.—ADMISSIONS, NATIONAL GUARD AND NATIONAL ARMY, SELECTED CAMPS

	September	October	November	December
National Guard—				
Camp Beauregard.....	2	32	466	1,299
Camp Wheeler.....	6	17	301	1,923
Camp Bowie.....	14	111	342	1,035
Camp Shelby.....	1	66	331	383
National Army—				
Camp Lee.....	1	7	276	990
Camp Travis.....	3	45	333	943
Camp Jackson.....	24	53	82	358
Camp Pike.....	4	1	123	344

In the camps mumps was present in slight degree in September. The number of cases had more than doubled in October, more than quadrupled in November over the preceding month, and increased in nearly the same ratio in the following month (Table 4). The maximum cases of admissions increased in many of the camps in January, 1918. After this there was a decline in number of new admissions.

The relative incidence of mumps at camp among the natives of the different states is indicated in Figure 3. It will be found instructive to compare this with Figure 1, showing the distribution of density of population. It appears at once that the densely populated states of southern New England and the Middle States are just those whose sons were most immune to mumps. On the other hand, the Southern Atlantic and Gulf States show a high incidence of mumps in states of sparse population. Louisiana and North Carolina have, for some

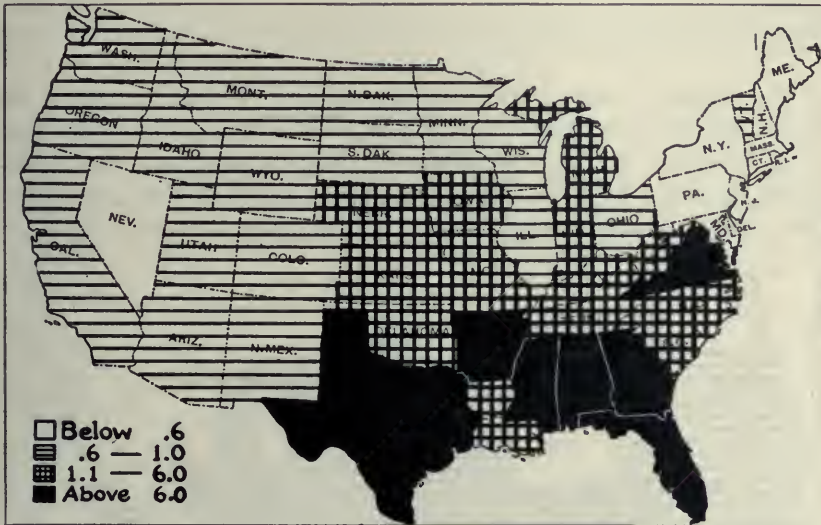


Fig. 3.—Map of the United States showing distribution of admission to sick report for mumps at National Army Camps, 1917, by state of nativity of enlisted men, rate per 100,000 of the adult male civil population of each state, aged 20 to 29 years, charted in four grades. The darker areas indicate greater incidence of the disease.

unexplained reason, a lower incidence for mumps than the sparseness of their population would warrant us in predicting. The relation between density of population and immunity breaks down if an attempt is made to apply it to the sparsely settled western areas, a result which may be in part due to the recent immigration into these states, which makes the divisor used (of current population instead of actual number born) too large, and hence the quotient too small.

The correlation between urbanity and admission for mumps is shown in Table 5. From this table the correlation was found to be  $-.58$ , which again is a rather large correlation.

TABLE 5.—CORRELATION BETWEEN ADMISSIONS FOR MUMPS BY STATE OF NATIVITY AND PERCENTAGE OF URBANITY OF THE STATE

Per Cent of Urbanity of States*	0 to 2.9	3 to 5.9	6 to 8.9	9 to 11.9	12 to 14.9	Deviation	Frequency
10 to 19.9	2	4	2	1	2	-30	11
20 to 29.9	..	5	3	..	2	-20	10
30 to 39.9	2	2	..	..	..	-10	4
40 to 49.9	5	4	..	..	..	0	9
50 to 59.9	5	1	..	..	..	..	6
60 to 69.9	3	..	..	..	..	..	3
70 to 79.9	2	..	..	..	..	..	2
80 to 89.9	1	..	..	..	..	..	1
90 to 99.9	3	..	..	..	..	..	3
Frequency.....	23	16	5	1	4	..	49

\* See Table 6 for names of states.

(c) *Lobar Pneumonia*.—Lobar pneumonia occurs either as a primary disease or secondary to measles and other epidemic diseases. It is, indeed, a tenable hypothesis that the symptoms of lobar pneumonia in young men of military age usually appear only after some event that has diminished resistance, such as disease of the respiratory

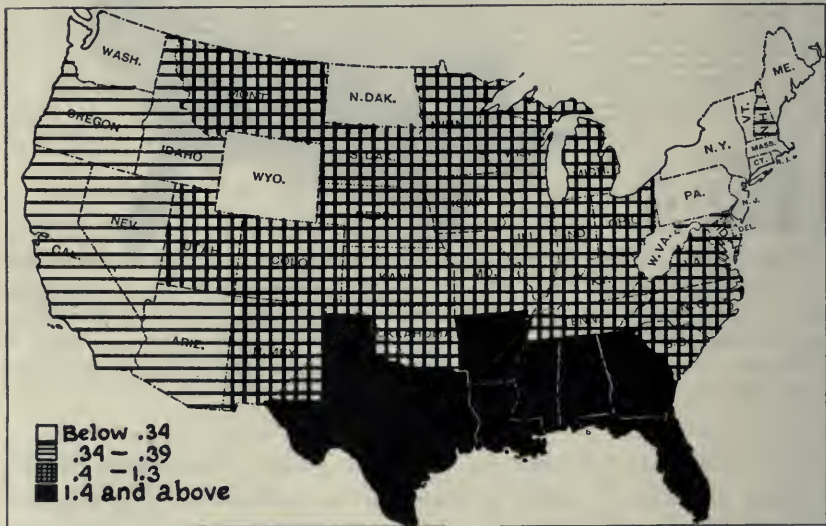


Fig. 4.—Map of the United States showing distribution of admission to sick report for lobar pneumonia (primary) in National Army camps, 1917, by state of nativity of enlisted men, rate per 100,000 of the adult male civil population of each state, aged 20 to 29 years, census of 1910, charted in five grades. The darker areas indicate the greater incidence of lobar pneumonia.

tract, overwork, or exposure. In the present section we shall consider, however, those cases of primary lobar pneumonia, that is, those for which no antecedent disease was reported.

The incidence of lobar pneumonia in the different camps varies greatly, as in the case of measles and mumps; camps which, like Bowie

(Texas), Wheeler (Georgia), Pike (Arkansas), Travis (Texas) drew from a rural territory had much lobar pneumonia, while camps which, like Devens, Wadsworth, Dix and Upton, drew from densely populated areas, had relatively few cases of lobar pneumonia.

These relations are brought out graphically in Figure 4, which shows the distribution of the different degrees of incidence of lobar pneumonia according to the nativity of the patients. One sees again that the densely populated area of Southern New England and Middle States have few cases of lobar pneumonia, while the Gulf States show high incidence. The very sparsely settled states of the Great Basin have an intermediate amount of lobar pneumonia among their recruits.

TABLE 6.—CORRELATION BETWEEN RATE OF ADMISSION FOR LOBAR PNEUMONIA BY STATE OF NATIVITY AND PERCENTAGE OF URBANITY OF THE STATE (BASED ON TABLE 11, P. 476, S. G. REP., 1917)

State	Per Cent. of Urbanity	0 to 0.50	0.51 to 1.00	1.01 to 1.50	1.51 to 2.00	2.01 to 2.50	2.51 to 3.00	3.51 to 4.00	4.01 to 4.50	4.51 to 5.00	5.01 to 5.5	Devia- tion	Fre- quency
Miss., Ark., S. D., N. Mex., N. C., S. C., Nev., Ala., W. Va., Okla. ....	10 to 19.9	..	2	7	1	1	..	..	..	..	..	0	11
Tenn., Ga., Ida., Va., Tex., Ky., Neb., Fla., Kan., Wyo. ....	20 to 29.9	..	2	3	3	1	..	..	..	..	1	0	10
La., Iowa, Ariz., Mont., Minn., Ind., Mo., Wis., Ore., Utah, Mich., Vt., Del. ....	30 to 39.9	..	..	2	2	..	..	..	..	..	..	0	4
40 to 49.9	1	5	3	..	..	..	..	..	..	..	..	0	9
Colo., Md., Me., Wash., Ohio, N. H. ....	50 to 59.9	..	3	3	..	..	..	..	..	..	..	0	6
Pa., Ill., Calif. ....	60 to 69.9	..	2	1	..	..	..	..	..	..	..	0	3
N. J., N. Y. ....	70 to 79.9	..	2	..	..	..	..	..	..	..	..	0	2
Conn. ....	80 to 89.9	..	1	..	..	..	..	..	..	..	..	0	1
Mass., R. I., D. C. ....	90 to 99.9	..	3	..	..	..	..	..	..	..	..	0	3
Frequency .....	.....	1	20	19	6	2	..	..	..	1	0	0	49

The correlation between incidence of lobar pneumonia and density of the states in which the patients were born is shown in Table 6. The calculation correlation coefficient from this table gives  $-0.37$ , a relatively high inverse correlation.

The reason for this relation between incidence of lobar pneumonia and density of states will be discussed later. In the present connection it is worth while to point out that there is no such marked differences in the age distribution of deaths from lobar pneumonia in civil life that has been shown in Table 1 in the case of measles. This is brought out in Table 7, which gives for three urban and four rural states the total number of deaths and the number of deaths occurring at successive years of life. The data have been taken from the morbidity statistics of the census of 1915. Besides the number of deaths occurring at each successive period of life, there is given the proportion that the deaths over ten years are to the total deaths in the state.

A comparison of the sums of the three urban states and the four rural states shows no obvious differences between them. It appears to be true that in urban states there is a slightly lower mortality from lobar pneumonia under thirty years and a slightly higher mortality over thirty years of age than in the case of rural states.

TABLE 7.—LOBAR PNEUMONIA: TOTAL NUMBER OF DEATHS AND TOTAL NUMBER OF DEATHS AT VARIOUS AGES IN THREE URBAN AND FOUR RURAL STATES

States	Total Deaths	Under 1 Year	1 Year	2 Years	3 Years	4 Years	5 to 9 Years	10 to 19 Years	20 to 29 Years	30 to 39 Years	40 to 49 Years	50 to 59 Years	60 to 69 Years	70 to 79 Years	80 to 89 Years	90 to 99 Years	100 Years and Over	Per Cent. of Deaths Over 10 Years
Mass. ....	3,224	310	169	50	31	16	45	79	175	279	372	421	556	482	211	27	1	
R. I. ....	374	30	15	3	7	5	8	9	23	34	45	72	63	47	11	2	0	81.82
Conn. ....	945	92	32	17	9	4	10	19	63	86	143	132	147	121	57	11	2	82.65
Urban.....	4,543	432	216	70	47	25	63	107	261	399	560	625	766	650	279	40	3	81.22
Kansas.....	620	75	26	9	4	6	7	27	40	54	39	76	99	112	41	4	1	79.52
Ky. (white)...	770	83	33	19	10	5	19	45	42	58	62	80	126	129	55	4	0	77.75
Maine.....	411	32	11	6	2	6	9	19	22	35	44	44	74	64	36	7	0	83.74
Va. ....	419	27	9	5	6	3	11	22	39	27	49	52	73	69	26	1	0	85.44
Rural.....	2,220	217	79	39	22	20	46	113	143	174	194	252	372	374	158	16	1	80.59

(d) *Cerebrospinal Meningitis*.—This disease is more important on account of its high case mortality than on account of its frequency. In the army of 1917, 31 per cent. of those men diagnosed as having cerebrospinal meningitis died. The total number of admissions was 971. If the camps be compared in respect to the incidence of cerebrospinal meningitis it is found that camps drawing from densely populated areas, such as Camps Upton, Dix, Devens and Wadsworth, stand at the bottom of the list, while Jackson, South Carolina, Beauregard, Louisiana, stand at the head of the list.

The details of relative incidence of cerebrospinal meningitis by state of origin of the different troops is shown in Figure 5. This figure is drawn up in a different fashion from the preceding one. The basis of the map is the relative frequency of occurrence of cerebrospinal meningitis in the different camps, that is, the morbidity rate. This morbidity rate is assumed to be distributed uniformly over the states that are tributary to the camp. The territory tributary to each camp is shown in Figure 6. This method conceals individual differences between adjacent states, but it brings out differences that are due to variations in diagnosis and reporting at the different camps. Thus, it seems probable that Camp Gordon drawing from Tennessee, Georgia and part of Alabama, had a relatively small amount of cerebrospinal meningitis, possibly through greater attention to the isolation of

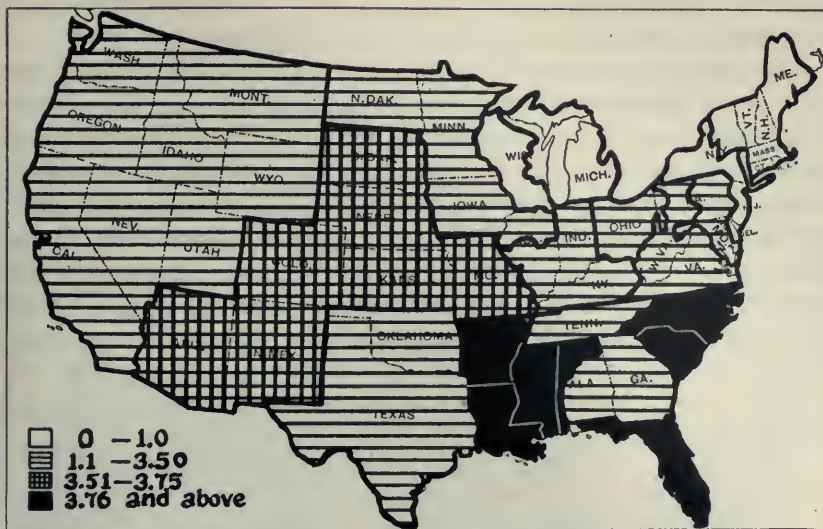


Fig. 5.—Map of the United States showing distribution of morbidity rate for cerebrospinal meningitis in National Army camps, 1917, by states from which the camps drew their troops, charted in four grades. The darker areas indicate greater incidence of the disease.

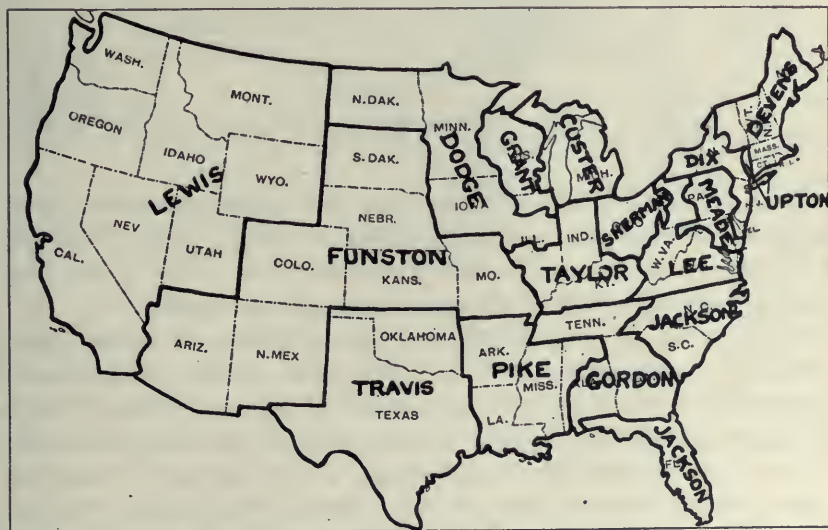


Fig. 6.—Map of the United States showing the territory tributary to each of the National Army camps, 1917.

incipient disease or carriers. Camp Pike, on the other hand, had a great deal of this disease which gained extensive headway in the camp after it had, probably, been imported from another camp.

If Figure 5 be compared with Figure 1, it will be seen at once that the areas of southern New England, New York and New Jersey show the greatest immunity to cerebrospinal meningitis, and are at the same time among the most densely populated areas. Michigan and Wisconsin, which are intermediate in population, had relatively few cases. On the other hand, the south Atlantic and Gulf States had, on the whole, a high incidence of cerebrospinal meningitis. The same is true of the western states, east and south of the Rocky Mountains. With certain irregularities and exceptional cases, therefore, it is generally true that recruits coming from the most thickly populated sections of the country were less susceptible to cerebrospinal meningitis than those coming from more sparsely settled areas.

TABLE 8.—CORRELATION BETWEEN RATE OF ADMISSIONS FOR CEREBROSPINAL MENINGITIS, TOTAL ADMISSIONS AND URBANITY OF STATE

Per Cent. of Urbanity of States	0 to 0.09	0.10 to 0.19	0.20 to 0.29	0.30 to 0.39	0.40 to 0.49	Devia- tion	Fre- quency
10 to 19.9	..	3	2	3	1	-30	9
20 to 29.9	1	2	2	1	2	-20	8
30 to 39.9	..	1	..	1	1	-10	3
40 to 49.9	2	2	1	..	1	0	6
50 to 59.9	..	1	2	..	..	10	3
60 to 69.9	..	3	..	..	..	4	3
70 to 79.9	2	..	..	..	..	..	2
80 to 89.9	..	..	1	..	..	..	1
90 to 99.9	1	..	..	..	..	..	1
Frequency.....	6	12	8	5	5	..	36

No cases from Alaska, Delaware, District of Columbia, Idaho, Maine, Vermont or Wyoming. Two cases or fewer from Montana, Nevada, New Hampshire, North Dakota, Rhode Island, Utah and Washington.

The correlation between admission for cerebrospinal meningitis and urbanity of the native state is shown in Table 8. The correlation has been calculated from this table and found to be  $-0.44$ , a somewhat smaller correlation than in the case of measles and mumps.

(a) *Scarlet Fever*.—There were no epidemics of scarlet fever among the army camps in 1917. The total number of admissions among troops in the United States was indeed only 1,966. The incidence of the disease differed a good deal in the different camps. Figure 7 shows the relative frequency of the disease among men coming from different parts of the country. Here, again, we note that men from New England and the more thickly settled parts of New York State had little scarlet fever, and the same is true of men at Camps Lee, Jackson, Gordan and Taylor. In the case of Camps Jackson and Gordon, at least, the areas drawn from were relatively sparsely settled. On the other hand, the states tributary to Camp

Pike give a high incidence of the disease, and the same is true of the states tributary to Camp Lewis, and both these territories are relatively sparsely settled. While it seems clear that pains taken at the camps to prevent the spread of scarlet fever is one important factor in determining its relative frequency in the different camps, still its infrequency among troops coming from the densely populated parts of the country suggests that such recruits had a relative immunity to scarlet fever. It may be added that since the colored race is relatively resistant to scarlet fever the small amount of scarlet fever among troops from the South Atlantic states is probably in part due to the considerable admixture of the colored race in recruits from those states.

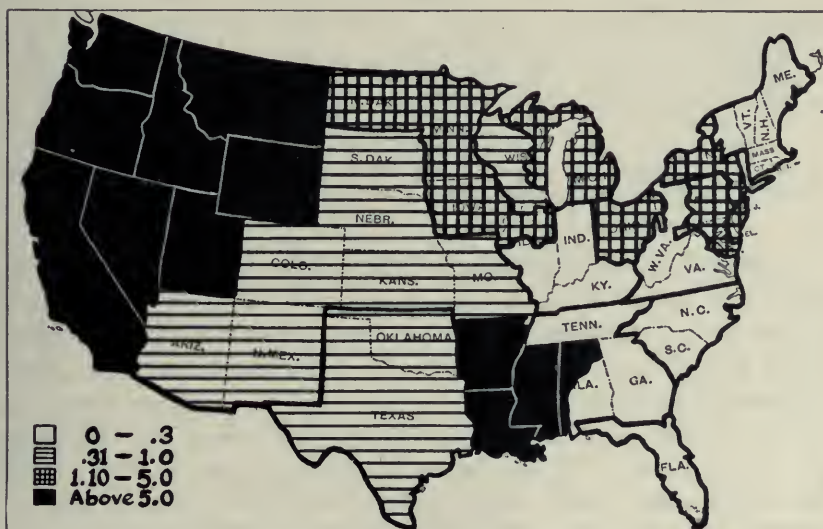


Fig. 7.—Map of the United States showing distribution of morbidity rate for scarlet fever in the National Army camps, 1917, by states from which each camp drew its troops, charted in four grades. The darker areas indicate the greater incidence of the disease.

(f) *Influenza*.—No detailed studies were made by the surgeon-general's office on the distribution by state of nativity of the cases of influenza that appeared in camp in 1917. A detailed study of the epidemic of influenza in 1918 is in course of preparation. Use may, however, be made of the imperfect and provisional telegraphic reports on influenza received by the surgeon-general's office during the autumn of 1918. An examination and tabulation of these reports indicates that even in the case of the pandemic influenza, camps that harbored chiefly recruits from rural states, in October and November, 1918, suffered worse than those that harbored mostly recruits from urban states. These facts are shown in Table 9.

TABLE 9.—COMPARISON OF FIVE CAMPS DRAWING CHIEFLY FROM URBAN STATES AND FIVE CAMPS DRAWING CHIEFLY FROM RURAL STATES, GIVING MORTALITY AND MORBIDITY IN RELATION TO THE INFLUENZA PANDEMIC, SEPT. 20 TO DEC. 31, 1918.  
FROM TELEGRAPHIC REPORTS TO THE SURGEON-GENERAL'S OFFICE (APPROXIMATE ONLY)

	Diseases			
	Influenza Admissions	Pneumonia Admissions	Deaths (All)	Admission Rate (Aver.)
Urban Camps—				
Wadsworth.....	1,382	474	88	2,204
Devens.....	5,519	1,912	822	3,443
Dix.....	5,917	2,290	821	1,879
Meade.....	9,696	2,937	809	2,483
Upton.....	9,383	1,288	410	3,287
Total.....	31,897	8,901	2,950	13,301
Rural Camps—				
Beauregard.....	4,426	1,134	444	4,177
Dodge.....	9,550	1,623*	718	3,709
Funston.....	13,617	1,946	911	2,400
Grant.....	9,656	2,687	1,086	2,406
Travis.....	6,905	2,562	221	4,393
Total.....	44,154	9,952	3,380	17,085

\* This included one missing report estimated as 500.

While too much stress may be paid on the precise results of the preliminary figures given in Table 9, still they suffice to indicate that the prevailingly rural camps (of which two were located in the South) had at least 25 per cent. more cases of influenza, 10 per cent. more pneumonia, 10 per cent. more deaths and 30 per cent. higher admission rate for all sickness than the prevailingly urban camps (of which one was in the South). It may be concluded, consequently, that in the influenza pandemic rural troops suffered more than urban troops.

### III. TOTAL EPIDEMIC DISEASES IN CAMPS

As a sort of summary of the preceding sections and for the purpose of supplying certain additional data, Table 10 has been drawn up. This gives the ratios of incidence of the mentioned diseases for October, November and December, 1917, for the sixteen National Army camps. By referring to Figure 6, compared with Figure 1, it will be easy to see which camps drew from a prevailingly rural and which from a prevailingly urban territory. A glance will show that the large ratios are apt to occur in the camps that draw from the sparsely settled areas east of the Mississippi river. The general relation which we have considered between the sparsely settled areas and incidence of communicable diseases does not, it will be noted, hold in detail for the territory west of the Mississippi river. Thus, Camps Funston and Lewis were not noteworthy for a large disease rate. This is probably

TABLE 10.—ANNUAL RATES PER 1,000 MEN FOR CERTAIN CAMPS BY SPECIAL DISEASES FOR OCTOBER, NOVEMBER AND DECEMBER, 1917. (ABSOLUTE NUMBERS ARE GIVEN IN TABLE 52, SURGEON-GENERAL'S REPORTS, 1918)

Camp	Bronchopneumonia				Lobar Pneumonia				Measles, Uncomplicated				Measles Complicated with Bronchopneumonia			
	Oct.	Nov.	Dec.	Total	Oct.	Nov.	Dec.	Total	Oct.	Nov.	Dec.	Total	Oct.	Nov.	Dec.	Total
Custer, Mich.	0.45	3.58	3.13	0.21	6.23	4.69	6.51	5.86	17.30	72.95	95.49	64.83	.....	.....	0.54	0.21
Devens, Mass.	0.51	0.52	1.14	0.71	2.02	3.13	4.02	3.58	0.90	14.75	73.79	29.84	.....	.....	.....	.....
Dix, N. J.	2.74	1.64	0.69	1.77	19.20	2.08	8.52	4.06	1.52	2.08	13.64	5.47	.....	.....	.....	.....
Dodge, Iowa.	0.57	2.34	2.27	1.61	15.41	22.58	33.15	24.33	10.97	43.26	172.64	68.47	0.55	0.55	0.39	0.39
Funston, Kan.	0.76	2.68	2.55	2.22	9.89	6.24	6.05	14.68	6.28	86.94	23.44	26.61	0.86	2.72	1.51	1.61
Gordon, Ga.	1.75	1.03	1.73	1.51	7.88	7.72	12.13	7.14	45.62	86.04	180.20	118.95	.....	0.45	7.65	3.49
Gordon, Ill.	0.94	12.59	7.43	7.03	3.77	9.32	11.34	9.06	1.75	6.69	80.30	26.18	.....	.....	1.16	0.34
Jackson, S. C.	.....	.....	5.31	1.78	0.46	7.25	16.38	8.15	98.03	402.33	95.77	102.82	.....	13.52	2.74	5.27
Lee, Va.	.....	.....	.....	.....	.....	.....	.....	.....	0.46	87.60	96.50	62.88	.....	0.43	3.54	1.33
Lewis, Wash.	2.28	3.31	2.06	2.56	10.48	10.60	8.22	9.78	3.59	13.58	27.06	14.55	.....	.....	0.34	.....
Meade, Md.	0.73	1.54	2.71	1.88	2.18	9.64	16.62	11.13	4.36	18.50	37.99	23.99	0.73	21.72	19.73	17.80
Pike, Ark.	2.14	7.82	16.18	9.39	30.45	62.56	65.11	53.88	490.46	793.22	439.60	690.33	10.68	.....	.....	.....
Sherman, Ohio.	0.78	2.62	3.98	2.50	10.56	20.22	24.23	18.52	3.52	17.22	53.88	25.52	.....	.....	.....	.....
Taylor, Ky.	3.23	0.54	6.77	3.47	17.76	11.36	25.96	18.25	48.14	292.74	193.00	177.62	2.15	8.66	12.98	7.85
Travis, Texas.	3.27	5.56	9.52	6.30	29.00	44.07	71.97	49.57	14.50	929.63	496.19	515.01	0.47	12.22	6.87	6.97
Upton, N. Y.	0.43	0.49	1.70	0.89	2.59	3.91	12.31	6.40	0.43	2.98	15.70	6.55	.....	0.49	1.27	0.60
Totals.	1.29	3.04	4.44	2.97	10.87	16.32	20.84	16.15	47.94	185.72	136.27	122.87	0.88	3.87	3.72	2.87

Camp	Measles Complicated with Lobar Pneumonia				Measles with Complications Other than Pneumonia				Cerebrospinal Meningitis (Epidemic)				Mumps			
	Oct.	Nov.	Dec.	Total	Oct.	Nov.	Dec.	Total	Oct.	Nov.	Dec.	Total	Oct.	Nov.	Dec.	Total
Custer, Mich.	.....	.....	.....	.....	.....	.....	.....	.....	2.08	.....	0.54	0.84	38.06	44.85	45.58	43.08
Devens, Mass.	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	1.34	0.45	.....	.....	5.37	2.83
Dix, N. J.	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	3.11	5.11	2.65
Dodge, Iowa.	.....	0.55	2.76	0.98	1.10	1.64	4.14	2.16	2.74	.....	8.29	3.34	4.39	31.76	82.87	36.49
Funston, Kan.	.....	0.39	0.76	0.34	0.29	2.34	0.38	0.92	1.52	8.17	0.38	4.38	9.99	8.17	3.40	7.46
Gordon, Ga.	.....	0.45	2.18	1.11	0.76	0.89	1.09	0.95	1.32	0.89	5.82	3.17	7.60	5.80	11.28	8.56
Grant, Ill.	.....	.....	.....	.....	.....	.....	.....	.....	0.44	2.37	0.38	1.17	29.32	4.63	10.98	15.94
Jackson, S. C.	1.41	3.73	1.61	1.61	1.89	21.44	8.60	10.55	.....	9.32	41.44	18.46	24.98	98.23	139.95	72.24
Lee, Va.	.....	.....	.....	.....	.....	.....	.....	.....	1.39	0.85	1.77	1.33	3.24	117.90	438.25	188.34
Lewis, Wash.	.....	1.28	2.66	1.33	0.33	2.14	1.77	1.83	0.98	2.98	4.45	2.78	4.90	12.92	25.09	15.11
Meade, Md.	.....	.....	0.34	0.11	0.33	0.39	1.03	0.56	.....	0.39	3.73	1.73	0.73	4.24	14.58	7.95
Pike, Ark.	8.55	13.47	16.97	13.42	4.81	15.64	11.44	11.03	2.14	6.52	5.13	4.77	0.53	53.43	135.75	69.77
Sherman, Ohio.	.....	.....	.....	.....	.....	.....	.....	.....	0.39	2.25	3.25	2.00	4.69	12.73	14.47	10.76
Taylor, Ky.	.....	3.25	0.56	1.28	0.39	21.65	4.51	9.31	0.89	7.58	4.51	4.20	8.61	27.05	24.83	20.08
Travis, Texas.	0.94	11.11	13.33	8.98	1.61	36.30	30.08	23.71	0.54	3.22	6.47	3.22	21.05	125.18	359.10	177.65
Upton, N. Y.	.....	.....	1.27	0.45	.....	.....	.....	.....	0.47	0.49	.....	0.15	0.43	1.96	23.34	8.93
Totals.	0.62	2.26	2.77	1.91	0.65	6.71	4.28	3.94	1.17	2.84	5.79	3.33	9.61	31.67	85.69	43.39

because soldiers in those camps were born in more crowded states than those whence they were recruited (see below).

The relation of the total epidemic diseases in camps to nativity is well brought out in Figure 8. This map combines admissions from primary lobar pneumonia; measles, simple or complicated; cerebro-spinal meningitis and German measles. The sum of these admissions for the natives of each state is divided by the total admissions for the corresponding state of nativity. The total, then, shows for the dif-

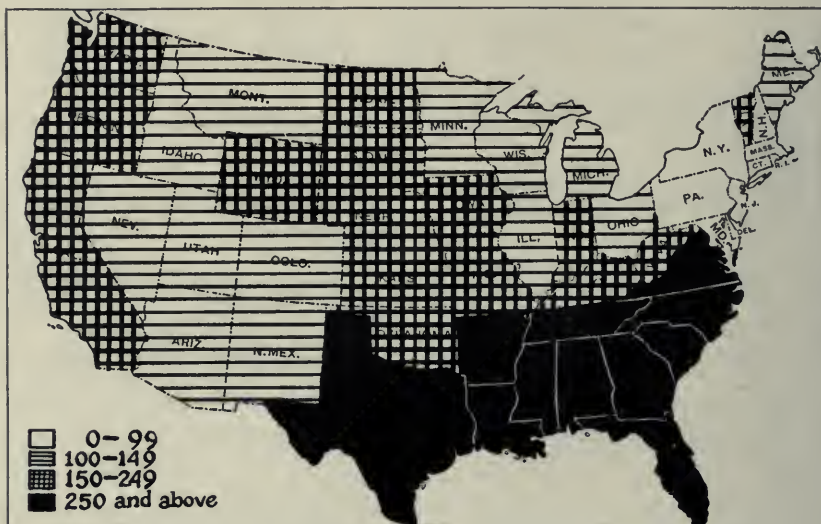


Fig. 8.—Map of the United States showing the sum of admissions to sick report for primary lobar pneumonia; measles, simple or complicated; cerebro-spinal meningitis and German measles. The chart gives for the different states the relative proportion of admissions to sick report which were for the named epidemic diseases. The table is drawn up by dividing the number of admissions in 1917 of the given diseases by nativity  $\times 1,000$  (Table 60, S. G. Rep., 1917) by total admissions by nativity (Table 10, S. G. Rep., 1917).

ferent states the relative proportion of admissions to sick report which were for the named epidemic diseases. The consistently high proportion in the Gulf and South Atlantic States is striking. The southern Central States and the great prairie region west of the Mississippi River, and the Pacific States come next; the densely populated New England States, the Middle States and Maryland, have the least.

Just why the sparsely settled states of the Great Basin showed such a small amount of infectious disease is a little doubtful. The most reasonable explanation is that a large proportion of natives were really born in more densely populated states. That this is so is shown by a little figuring. Assuming that the place of birth is given correctly, then we have a curious result. For the men of the draft age were

children approximately of 5 to 14 years of age at the time of the census of 1900 — 17 years of age before the draft. According to that census there were 243,500 such children in Wisconsin. The admission to sick report of natives of Wisconsin in 1917 was 10,700, or 4.4 per cent. of the children of Wisconsin in 1900. Similarly, the admissions to sick of natives of Tennessee was 6 per cent. of the number of children in that state in 1900. These two states are those of relatively stable population during the last seventeen years. In contrast to them we have in Oklahoma in the year 1900, 51,000 children and in 1917 an admission to sick report of 5,793 "natives" from that state, or 11.4 per cent. Now, Oklahoma is the state that has shown the greatest growth in the last seventeen years, and this has the greatest ratio of "natives" who were sick to actual natives of military age. This suggests strongly that many early immigrants to Oklahoma were classified at camp hospitals as natives of the state. They probably came from sparsely settled farming districts and so had the slight immunity represented by the chart.

Much the same confusion between nativity and early migration is found in the camp returns as to the nativity of the sick assigned to the states of the Great Basin. For we find in all of these states an abnormally high proportion of admissions to sick report divided by children from 5 to 14 years living in those states in 1910. Thus, for Arizona this proportion is 11.4 per cent.; in Utah, 11.1 per cent.; in Nevada, 10.6 per cent.; in Idaho, 11.5 per cent., and in Montana, 10.7 per cent. The reason why these rates are approximately double the rates of Wisconsin and Tennessee is that many of the men called natives of these states were merely early migrants to these states. They were not really born in them, but probably in some more densely populated states where they passed their early years and in which they secured a childhood immunity.

## 2. HYPOTHESES

1.—To explain the relation between immunity from disease and density of settlement of the territory in which troops were born, there are four hypotheses that come to mind and which deserve to be tested. The first hypothesis is that the recruits coming from densely populated areas are immune from a given disease because they have already had the disease. This hypothesis was formulated by Surgeon-General Gorgas when he visited Camp Wheeler at the height of the epidemic of measles on Nov. 26, 1917. He said: "I think the reason for the measles affecting so severely this particular camp is the fact that the men came from the surrounding southern states which are sparsely settled, and, therefore, the inhabitants do not, as a rule, have measles

in childhood." On this hypothesis the cause of immunity is the antecedent incidence in the soldiers of the specific diseases — measles, mumps, lobar pneumonia, cerebrospinal meningitis and scarlet fever, as the case may be.

The foregoing hypothesis encounters certain difficulties. At least, it is hardly feasible to regard it as sufficient to cover all of the cases of communicable diseases. Thus, the distribution of lobar pneumonia by state of nativity resembles closely, as we have seen, the distribution of measles and mumps. That is, in all cases the southern New England and Middle States are relatively immune and the Gulf States are relatively susceptible. Yet one cannot explain this distribution of immunity in the case of lobar pneumonia on the hypothesis that the immune persons had already had pneumonia during their early life. Lobar pneumonia is not a sufficiently frequent cause of morbidity in childhood and youth to warrant such a conclusion. As Table 7 shows, the rate of mortality from lobar pneumonia is relatively low throughout childhood and slightly lower in urban than in rural districts. Similarly, the states that show immunity from measles and mumps likewise show immunity to cerebrospinal meningitis, and contrarywise, the Gulf and South Atlantic States are susceptible. But, again, cerebrospinal meningitis is hardly so frequent a disease of early life as to warrant us in saying that the soldiers from the immune areas had acquired immunity to the disease by having had it in their youth. While it is true that measles (as measured by mortality) is much commoner during childhood in urban than in rural states, yet this is not true of scarlet fever, lobar pneumonia and meningitis. These facts are brought out in Table 11, taken from the census "Morbidity Statistics" from 1913 to 1916 consolidated.

TABLE 11.—"MORTALITY STATISTICS" FROM CIVIL POPULATION, U. S. CENSUS, 1913 TO 1916. PROPORTION OF PERSONS WHO DIED FROM CERTAIN DISEASES UNDER TEN YEARS OF AGE TO TOTAL DEATHS FROM THE DISEASE

Disease	Urban States	Rural States
Measles.....	0.960	0.740
Scarlet fever.....	0.824	0.844
Lobar pneumonia.....	0.187	0.202
Meningitis.....	0.680	0.754

Consequently, while the hypothesis of immunity through incidence of the disease in early years applies to measles and mumps, it does not apply generally.

2. A second hypothesis is that there has been a selective elimination of susceptible individuals in the more densely populated regions and that in the less densely populated regions this selective elimination

has been less rigid. On this hypothesis recruits coming from the larger cities and the densely settled states differ in their constitution from those coming from the rural districts and the less dense populated states, in that the susceptibles have been more largely eliminated by death. Consequently, they constitute a more resistant population than do recruits from the sparsely settled states.

The foregoing hypothesis cannot, however, be applied generally; if, indeed, it has any validity at all. In the first place, certain of the diseases to which the men from the New England and Middle States showed greatest immunity are not more apt to kill children in cities than in rural districts. This is true, for example, in the case of cerebrospinal meningitis, the epidemics of which are quite as apt to occur in small towns and villages as in larger cities (see Table 10). Again, although there is clear resistance to mumps in soldiers from the Northeastern States, still mumps rarely kills children and hence cannot act by selective annihilation to diminish the susceptibility of the population.

3.—A third hypothesis which has been suggested is that certain diseases which are widespread throughout the South, like malaria, hookworm, pellagra and intestinal parasites have increased susceptibility. This would account for the relatively small morbidity among troops from the sparsely settled states of the Central Basin, but would not account for the higher morbidity of the Northern States west, as compared with those east, of the Alleghenies. Also, we have no experimental evidence that such diseases increase susceptibility to measles, mumps, scarlet fever and the others.

4.—A fourth hypothesis is that recruits coming from large cities and other densely populated areas have acquired a general immunity to infectious or communicable diseases. This hypothesis assumes that any one of the communicable diseases leaves the body in a state of heightened resistance to all micro-parasites, possibly through a condition of persistent hyperleukocytosis. This hypothesis has, indeed, received scientific standing through the researches of Jobling<sup>1</sup> and others. If this hypothesis is valid, we should expect to find that resistance to communicable diseases runs fairly parallel with the density of population or of the living conditions in which persons are found.

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1. Jobling, J. W., and Petersen, W.: The Nonspecific Factors in the Treatment of Disease, *J. A. M. A.* **66**:1753, June 3, 1916.

2. Jobling, J. W.: The Influence of Nonspecific Substances on Infections, *Arch. Int. Med.* **19**:1042, June, 1917.

The history of epidemics is of interest in this connection. Thus, in the large epidemic of poliomyelitis in New York City in 1916, it was found that the densely populated areas of Manhattan showed a lower incidence than the less densely populated areas of Brooklyn and Queens. Thus the rates per 100,000 population were, in Manhattan, 125; in Brooklyn, 246; in Queens 318.<sup>3</sup> It is true that poliomyelitis was constantly present in preceding years and that the rate was, in these earlier years, higher in Manhattan and Bronx than in Brooklyn and Queens; but the rate was a small one, less than 2 per 100,000 on

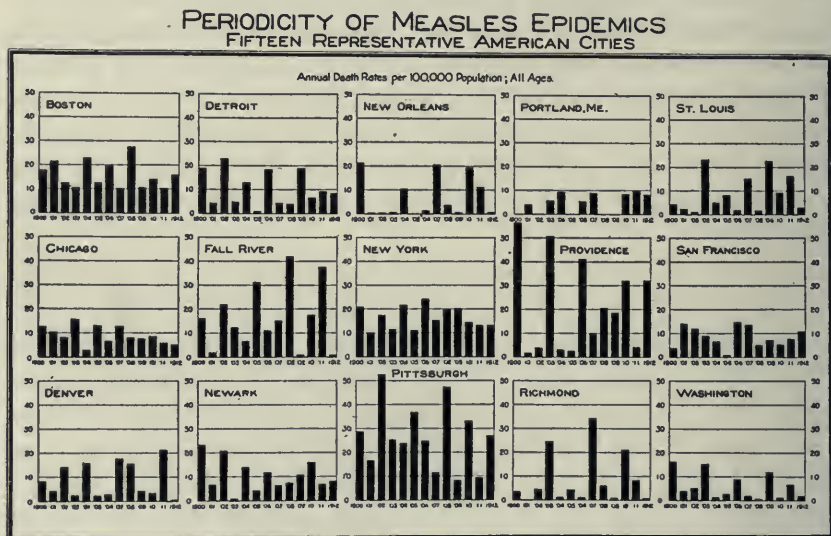


Fig. 9.—Graph showing for fifteen representative American cities the periodicity of epidemics of measles (furnished by the Prudential Life Insurance Company).

the average for the less sparsely populated burroughs; less than 5 per 100,000 on the average for the more densely populated burroughs. These low rates were clearly not sufficient to cause the difference in immunity to the great epidemic between Manhattan on the one hand and Queens on the other.

It has, indeed, been shown, as result of studies made by the New York City Department of Health,<sup>4</sup> that the Russian and Austrian population of that city, living under the most crowded and unhygienic conditions, are most resistant to the various diseases of infancy, so that they have a relatively low mortality.

3. Monthly Bulletin California State Board of Health, January, 1919, p. 227.

4. Guilfooy, W. H.: The Influence of Nationality upon the Mortality of a Community, Department of Health of the City of New York, Monograph No. 18, November, 1917.

Another phenomenon which speaks for the conclusion that "non-specific therapy" has given a general immunity for epidemics is found in the history of epidemics. It is a common experience that after an

TABLE 12.—DEATH RATES PER 100,000 OF POPULATION IN REGISTRATION CITIES. FROM "MORTALITY STATISTICS," UNITED STATES BUREAU OF THE CENSUS, 1912-1916

	Measles	Scarlet Fever	Whooping Cough	Total		Measles	Scarlet Fever	Whooping Cough	Total
District of Columbia:					Birmingham, Ala.:				
1912.....	1.6	1.6	8.6	11.8	1912.....	13.2	2.2	9.9	25.3
1913.....	7.7	5.2	1.2	14.1	1913.....	7.3	1.0	16.7	25.0
1914.....	....	0.4	2.4	2.8	1914.....	11.9	6.0	19.9	37.8
1915.....	2.3	3.1	3.1	8.5	1915.....	5.5	20.2	0.9	26.6
1916.....	1.9	1.9	4.9	8.7	1916.....	....	1.8	1.8	3.6
Omaha, Neb.:					Bridgeport, Conn.:				
1912.....	0.8	3.9	14.0	18.7	1912.....	6.4	17.4	9.2	33.0
1913.....	0.8	10.7	2.3	13.8	1913.....	13.4	26.8	7.1	47.3
1914.....	1.5	12.8	7.5	21.8	1914.....	28.6	16.5	18.2	63.3
1915.....	8.0	14.1	10.4	32.5	1915.....	6.8	7.6	19.4	33.8
1916.....	1.8	33.8	1.8	37.4	1916.....	15.6	3.3	12.3	31.2
Atlanta, Ga.:					Springfield, Ill.:				
1912.....	9.9	1.8	4.5	16.2	1912.....	5.5	....	14.6	20.1
1913.....	6.1	....	10.4	16.5	1913.....	31.9	1.8	24.8	58.5
1914.....	10.1	0.8	8.4	19.3	1914.....	....	9.2	7.3	16.5
1915.....	1.6	0.8	8.7	11.1	1915.....	3.9	10.7	1.8	16.4
1916.....	0.8	1.5	2.3	4.6	1916.....	8.9	6.5	16.4	31.8
Fall River, Mass.:					Richmond, Va.:				
1912.....	1.6	7.3	4.9	13.8	1912.....	1.2	....	2.4	3.6
1913.....	58.9	21.8	11.3	92.0	1913.....	19.0	4.7	8.3	32.0
1914.....	2.4	9.6	17.5	29.5	1914.....	1.2	2.3	21.1	24.6
1915.....	14.2	4.7	21.3	40.2	1915.....	....	1.0	....	1.0
1916.....	30.4	1.6	13.2	45.2	1916.....	15.9	3.0	13.9	32.8
Los Angeles, Calif.:					New Haven, Conn.:				
1912.....	0.3	2.2	9.8	12.3	1912.....	18.7	5.7	12.9	46.3
1913.....	13.7	3.3	6.3	23.3	1913.....	1.4	8.5	7.8	17.7
1914.....	1.4	1.2	2.6	5.2	1914.....	21.5	4.8	4.8	31.1
1915.....	4.2	2.2	2.0	8.4	1915.....	12.2	3.4	6.8	22.4
1916.....	1.9	1.4	9.3	16.1	1916.....	5.3	6.7	12.7	24.7
Minneapolis, Minn.:					Jersey City, N. J.:				
1912.....	3.4	4.6	2.8	10.8	1912.....	5.3	9.2	12.8	27.3
1913.....	6.0	18.6	4.5	29.1	1913.....	10.4	14.3	12.9	37.6
1914.....	2.6	26.1	12.8	41.5	1914.....	4.4	7.5	4.1	16.0
1915.....	3.7	3.1	4.8	11.6	1915.....	17.7	5.0	13.0	35.7
1916.....	20.4	4.4	7.4	32.2	1916.....	5.9	3.9	5.2	15.0
Oakland, Calif.:					New Haven, Conn.:				
1912.....	3.0	....	9.6	12.6	1912.....	18.7	5.7	12.9	37.3
1913.....	....	1.1	1.1	1.2	1913.....	1.4	8.5	7.8	17.7
1914.....	15.6	2.9	14.5	33.0	1914.....	21.5	4.8	4.8	31.1
1915.....	2.6	0.5	10.0	13.1	1915.....	12.2	3.4	6.8	22.4
1916.....	....	....	2.5	2.5	1916.....	5.3	6.7	12.7	24.7
Pittsburgh, Pa.:					Waterbury, Conn.:				
1912.....	27.7	11.1	10.3	49.1	1912.....	9.0	7.7	2.6	19.3
1913.....	27.9	29.1	14.5	71.5	1913.....	17.4	3.7	13.7	34.8
1914.....	9.1	34.4	7.8	51.3	1914.....	3.6	17.0	7.3	27.9
1915.....	13.0	9.7	7.7	30.4	1915.....	7.1	....	11.8	18.9
1916.....	23.4	3.8	16.7	43.9	1916.....	13.8	....	5.7	19.5
San Francisco, Calif.:									
1912.....	11.3	0.7	5.3	17.3					
1913.....	1.9	4.3	3.8	10.0					
1914.....	10.7	1.2	12.5	24.4					
1915.....	5.0	1.8	4.8	11.6					
1916.....	1.3	1.6	3.8	6.7					

epidemic year communities will be exceptionally free from epidemics for a year or two later. This result is illustrated in the chart (Fig. 9, furnished by the Prudential Insurance Company) of annual death rates from measles per 100,000 of the population of fifteen representative

cities. It is seen that great maximums (as at New Orleans, Fall River, Providence and Richmond) are followed by minimums in the next year. The large cities (New York, Chicago, Boston and St. Louis) show less extreme fluctuations, because such cities are really groups of cities, and the epidemic does not spread over all of the territory included in them during a single year.

This periodicity in the recurrence of epidemics is generally explained on the hypothesis that all persons susceptible to the particular epidemic diseases have acquired that disease during the first year of the epidemic. But this is not the whole story. For not only is the disease which became epidemic uncommonly scarce in the following year, but also some other epidemic diseases. Thus, if the mortality from measles, scarlet fever and whooping cough in cities from 50 to 250,000 inhabitants be studied in successive years, it will be found a common, if not the usual, event that the year following an epidemic of measles will be one of exceptionally small mortality for whooping cough or scarlet fever.

Data for this study have been obtained from the mortality statistics, Table 3, of the United States Bureau of the Census, years 1912 to 1916 inclusive. The results from certain selected cities are tabulated in Table 12. The mortality curve for all these diseases combined tends to crawl up to a maximum and then fall suddenly in one year (or sometimes two) to a minimum and then gradually in successive years to advance to a new maximum (Fig. 10). Thus, in Figure 10 we see that the great epidemic of measles in Bridgeport in 1914 was followed in 1915 by a minimum, not only of measles, but also of scarlet fever (1915 to 1916). In Fall River the measles epidemic of 1913 was followed by a minimum of measles in 1914, and a declining rate in scarlet fever. The whooping cough maximum comes two years later. In Atlanta, Ga., Los Angeles, Calif., and Springfield, Ill., there is a similar history.

A similar result appears in the history of epidemics in our army camps. German measles replaced common measles in Camp Lewis during the autumn of 1917. An epidemic of measles, like that of 1917, was anticipated in the autumn of 1918. The camps contained new recruits among whom was much susceptible material. Measles was present, as well as mumps, scarlet fever and cerebrospinal meningitis, yet they did not spread. There were fewer admissions on account of measles in the camps during the week ending Oct. 11, 1918, when the influenza epidemic was at its height, than during the summer week ending August 30. Some meningitis appeared as the crisis of the influenza was passing — and this may be regarded as a complication

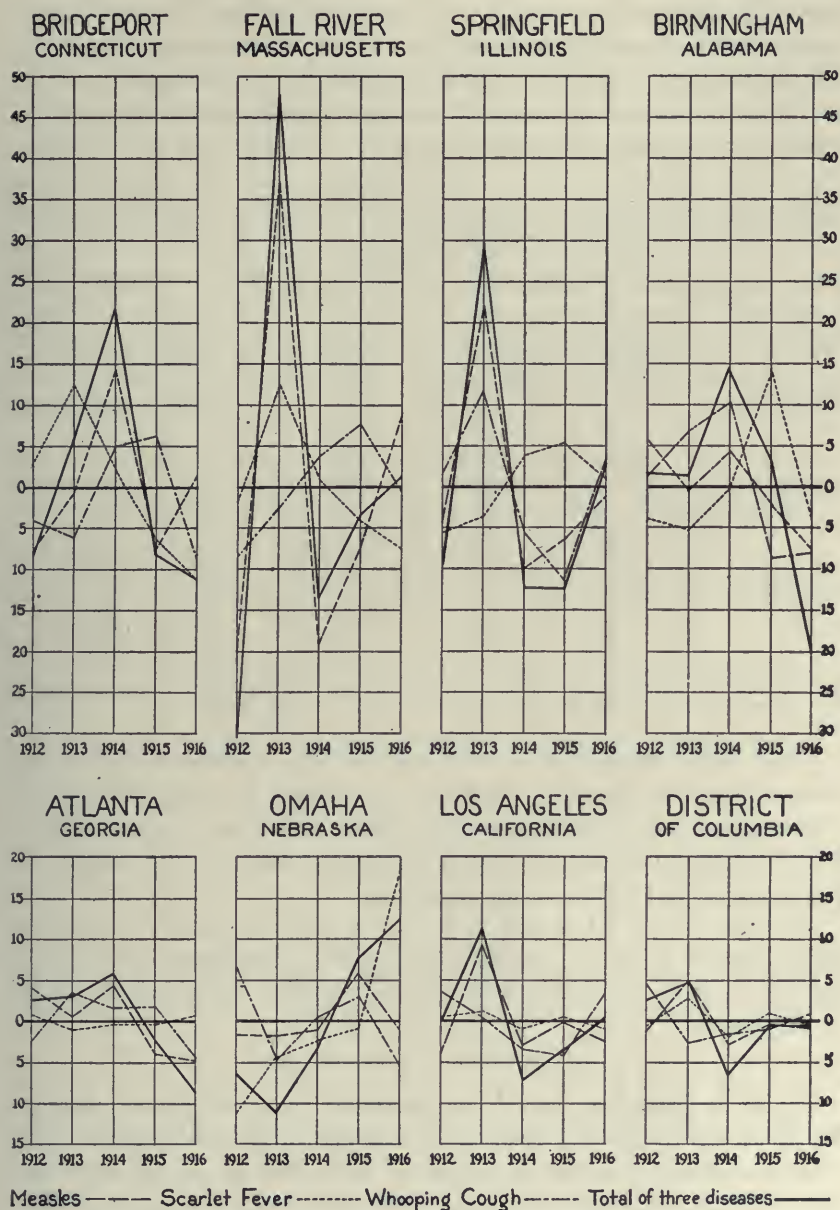


Fig. 10.—Graphs showing for eight cities the deviations in mortality rate from the average mortality rate for the years 1912 to 1916, inclusive. Curves are given for measles, scarlet fever, whooping cough and the sum of mortality from these three diseases.

of the influenza — but it never became epidemic. In Camp Hancock alone (in November) was there any important outbreak of scarlet fever. While the influenza pandemic was active and afterward (except for complications of influenza), the morbidity from contagious disease at the camps was rather low. This is indicated by the following table, based on the weekly telegraphic reports to the surgeon-general's office.

TABLE 13.—COMPARISON OF SICKNESS IN CAMPS FROM MEASLES, MENINGITIS AND SCARLET FEVER DURING NOVEMBER, 1917, AND 1918 (ANNUAL RATE PER 1,000 FOR SPECIAL DISEASES)

Disease	1917			1918	
	Week Ending	National Guard	National Army	Divisional Camps Week Ending	
Measles.....	Nov. 2	151	98	Nov. 1	18
	9	451	164	8	28
	23*	534	167	22	40
	30	300	123	29	35
	Dec. 7	368	163	Dec. 6	31
Meningitis.....	Nov. 2	0.4	2.7	Nov. 1	3.3
	9	1.1	2.9	8	1.6
	23	3.7	5.6	22	1.0
	30	3.8	3.2	29	0.4
	Dec. 7	5.4	4.1	Dec. 6	0.7
Scarlet fever....	Nov. 2	2.8	0.7	Nov. 1	1.0
	9	1.4	0.7	8	10.0
	23	2.1	3.6	22	19.4
	30	1.6	9.5	29	8.3
	Dec. 7	1.1	9.7	Dec. 6	1.8

\* Report for week ending November 16 not available at this writing.

The extraordinarily low rate for measles in 1918 is sufficiently evident; that for meningitis, though less striking, is none the less real. The rate for scarlet fever was temporarily raised in November (9 to 23), 1918, by conditions at Camp Hancock, otherwise the number of cases of scarlet fever in camps was small.

In view of the foregoing facts, the fourth hypothesis formulated above should be kept in mind as a possible explanation of the high resistance shown by troops coming from the more densely settled parts of our country.

#### SUMMARY OF CONCLUSIONS

1. In mobilization camps, communicable diseases have produced the least admission and death rate in those camps which drew from areas that were prevaillingly urban. The highest morbidity and mortality rates have been from camps that drew from the sparsely populated areas of the Southern Atlantic and Gulf States, and to a less striking extent from the sparsely settled states of the West.

2. The foregoing conclusion is based upon the studies made of measles, mumps, lobar pneumonia, cerebrospinal meningitis, scarlet fever and influenza.

3. The commonest explanation of this relation is that recruits from prevaillingly urban territory had acquired immunity through having had the disease in their youth. This hypothesis does not cover the case of the rarer diseases of childhood, such as cerebrospinal meningitis.

4. Another hypothesis is that the immunity is due to a selective elimination of susceptibles. It is assumed to be greater in densely populated than sparsely populated areas. This hypothesis fails, however, to account for immunity in the case of mumps which does not kill children.

5. Another hypothesis is that life in urban communities produces a general resistance to disease of which the observed resistance to measles, mumps, lobar pneumonia, cerebrospinal meningitis, scarlet fever are only special instances. Many collateral facts speak strongly for this hypothesis.

# PATHOLOGIC ANATOMY AND BACTERIOLOGY OF INFLUENZA \*

EPIDEMIC OF AUTUMN, 1918

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CAMP ZACHARY TAYLOR, KY.

In this paper the results of our studies on the pathologic anatomy and bacteriology of influenza during the epidemic of the fall of 1918 at Camp Zachary Taylor and Camp Knox, Kentucky, are presented.

Necropsies, with routine bacteriologic cultures, were performed throughout the entire epidemic, so that a fairly definite picture of its various stages could be formed. The present investigation has been limited to 126 definitely proven fatal cases of influenza. These were selected from a considerably larger number by ruling out all patients who clinically gave evidence of preexisting disease, such as tuberculosis, measles, etc., or where such evidence was found at the necropsies. Thus the morbid changes encountered may be looked on as primarily representing the end-results of the virus of influenza and its commensals.

No attempt has been made to give even a nearly complete bibliography, but for the purpose of comparison a limited number of references are cited. A great aid in this has been the exhaustive monograph of Leichtenstern-Sticker,<sup>1</sup> which deals with the pandemic of 1889 and the succeeding years. However, the original sources, as far as possible, have been consulted, since the monograph cited is primarily clinical. The work of Kuskow,<sup>2</sup> who studied forty undoubted cases of influenza in 1892, at Petrograd, deserves special mention, since it represents the most detailed anatomic work of that period. The present European epidemics have been summarized by the British

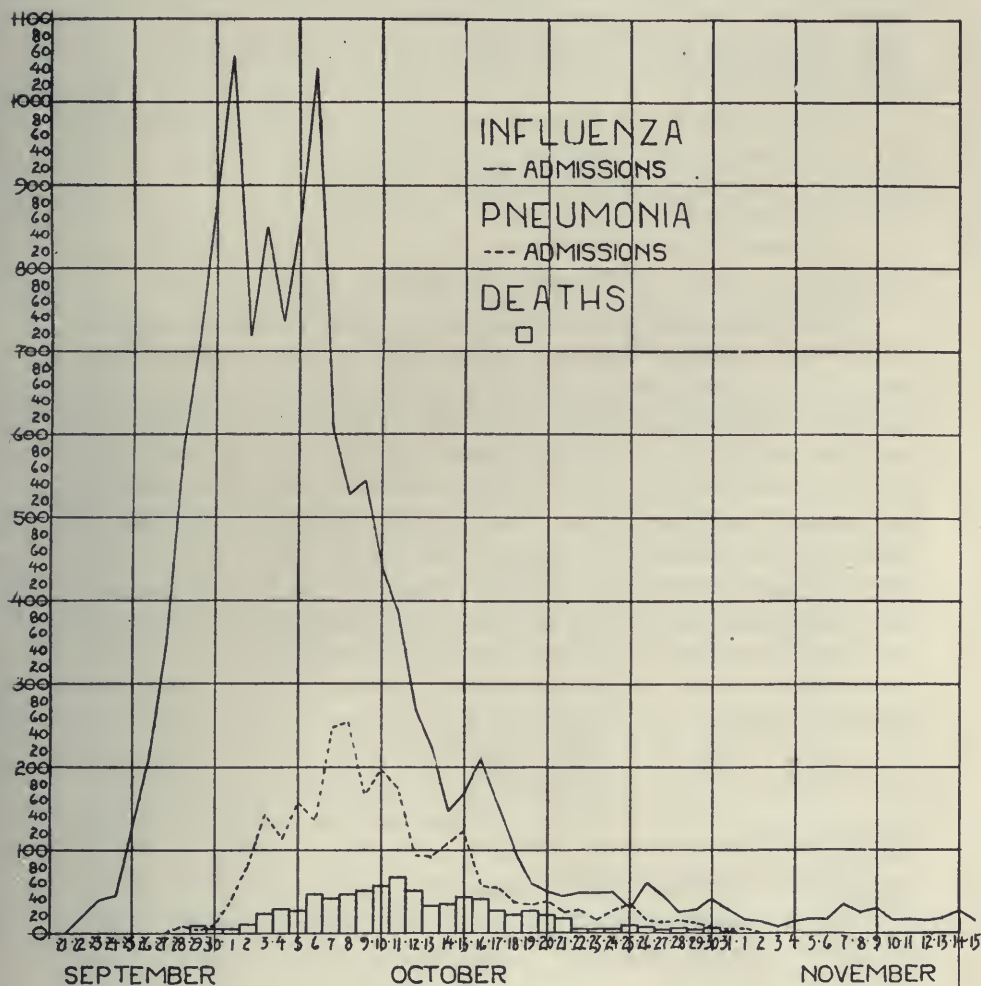
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\* From the Cantonment Laboratory, Base Hospital, Camp Zachary Taylor, Ky.

1. Leichtenstern, Otto: *Influenza*, Ed. 2, by George Sticker. Wien. u. Leipzig, Alfred Hoelder, 1912.

2. Kuskow, N.: *Zur pathologischen Anatomie der Grippe*, Virchow's Arch. **139**:406, 1895.

commission.<sup>3</sup> Most of the American literature is very recent and readily accessible, and for that reason only such quotations are made as apply more directly to the subject under discussion. An examination of the literature of both the present and the preceding pandemics will bring out that most writers have confined themselves to the dis-



ease changes in the respiratory tract, and that the disease seems to have varied greatly in virulence and its manifestations. The anatomic changes described at different times and places are often quite dis-

3. Abstracts of Foreign Literature Compiled by British Medical Research Committee, J. A. M. A. 71:1573 (Nov. 9) 1918.

similar. On the other hand, it is noteworthy that Lubarsch<sup>4</sup> and Hansemann (Report of British Commission) comparing the organs preserved since the preceding epidemic with those obtained from recent fatal cases, insist on the essential similarity of the lesions.

*Time of Epidemic.*—The pandemic manifested itself here first, Sept. 22, 1918, reached its height October 31, slightly declined again, reaching an apex comparable to the first on October 5, and terminated about November 15. Since this time only a small number of cases have occurred.

The first death due to influenza occurred September 28. The death curve gradually rose, reaching its highest point (seventy cases) October 5, and then gradually declined. (Graph 1.)

#### MORBIDITY AND MORTALITY FROM INFLUENZA AMONG WHITES AND NEGROES

The average aggregate population of this camp and of Camp Knox during the influenza epidemic was 58,000. Of these, 5,500 were negroes. A considerable discrepancy in the morbidity and mortality rate was observed between the two races (Table 1.) The number of cases of influenza per 1,000 population was 231 for the whites and seventy for the negroes. The number of deaths per 1,000 population was sixteen for the whites and seven for the negroes, but the number of deaths per 100 cases of influenza was 6.8 for the whites and 10.2 for the negroes. It shows, then, that while the incidence of influenza was considerably less among the colored soldiers, the mortality among those that contracted the disease was considerably higher.

TABLE 1.—MORBIDITY AND MORTALITY FROM INFLUENZA AMONG WHITES AND NEGROES, SEPT. 22, 1918, TO DEC. 1, 1918

	Total	Whites	Negroes
Average population .....	58,597	53,031	5,566
Morbidity—			
Actual number of cases of influenza.....	12,640	12,249	391
Number cases of influenza per 1,000 population.....	216	231	70
Mortality—			
Actual number of fatal cases.....	871	831	40
Number of deaths per 100 cases of influenza.....	6.9	6.8	10.2
Number of deaths per 1,000 population.....	15	16	7

There are three possible explanations for this discrepancy: exposure to infection, immunity and anatomic differences. Exposure may be dismissed, since practically all men were equally exposed. Immunity does not seem to us to play any part here, since once the disease was

4. Lubarsch: Die Anatomischen Befunde, von 14 tödtlich verlaufenden Fällen von Grippe, Berl. klin. Wchnschr., **55**:771, 1918. (Quoted by British Commission.)

contracted the mortality among the colored race was higher. It was observed in this camp throughout the past two years that various acute respiratory infections, such as catarrh of the nasal sinuses, were relatively uncommon among the colored soldiers and the explanation seemed to be that the rarely obstructed upper air passages of the negro afforded a good defense against lodgment of micro-organisms. This would hold true, of course, only for the individuals with more pronounced African features, disappearing with increased admixture of white blood. Opie<sup>5</sup> and his co-workers found negroes only about half as frequently infected as whites.

#### DURATION OF DISEASE

Eight patients, or 6.7 per cent., died within the first 5 days; average duration, 4.3 days.

Forty-nine patients, or 40.8 per cent., died within 6 to 10 days; average duration, 8.2 days.

Thirty-one patients, or 25.8 per cent., died between 11 and 15 days; average duration, 12.8 days.

Thirteen patients, or 10.8 per cent., died between 16 and 20 days; average duration, 17.5 days.

Nineteen patients, or 15.8 per cent., died after 20 days; average duration, 25.3 days.

In one case the duration of the disease was not obtainable. The average duration for the entire series was fourteen days. Lyon<sup>6</sup> found the average duration of life in his fifty-six cases to be 12.4 days. In five cases the disease exceeded forty days in duration. These, however, were typical influenza patients and may be looked on as having suffered from the chronic form of this disease. We shall describe the anatomic and bacteriologic findings of these chronic cases in a separate part of this communication. Otherwise, all the statements made apply to the 121 cases of acute influenza.

The relation of the duration of the disease to the period of epidemic was estimated (Table 2). For this purpose the entire epidemic was divided into five periods, generally of ten days each, except the last, which comprises the more scattered forms occurring in November and December. The table shows that of the forty-two cases necropsied during the first ten days after the first death of influenza had occurred, the average duration of the disease was 10 days. In the second period,

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5. Opie, Eugene L., Freeman, Allen W., Blake, Francis G., Small, James C., Rivers, Thomas M.: *Pneumonia Following Influenza* (Camp Pike, Ark.), J. A. M. A. **72**:557 (Feb. 22), 1919.

6. Lyon, M. W., Jr.: *Gross Pathology of Epidemic Influenza at Walter Reed General Hospital*, J. A. M. A. **72**:924 (March 29), 1919.

it rose to 13.6 days, in the third to 16.6, in the fourth to 16.7 days. In the fifth period it dropped to 13.1 days. This last period, as stated, comprises the time when the disease had lost more or less of its epidemic character. The difference in the duration of disease as the epidemic progressed is doubtless due to the fact that the most susceptible patients succumbed first, and that the least susceptible resisted a longer period. The duration of disease during the fifth period is more difficult to explain, but it may have been due to the incoming of non-exposed troops, or to fewer precautions taken by individuals because of the belief that the epidemic was over. Later we will show that the bacterial findings of this period approximated those of the earlier stages of the epidemic. It should also be remarked that at this time there occurred a particularly severe outbreak of the disease in the neighboring town of Louisville.

TABLE 2.—RELATION OF DURATION OF DISEASE TO PERIOD OF EPIDEMIC

	Duration of Disease										Total Number of Cases	Average Duration in Days
	1 to 5 Days		6 to 10 Days		11 to 15 Days		16 to 20 Days		More than 20 Days			
	No. of Cases	Average Duration in Days	No. of Cases	Average Duration in Days	No. of Cases	Average Duration in Days	No. of Cases	Average Duration in Days	No. of Cases	Average Duration in Days		
First period: Sept. 30 to Oct. 9	5	4.4	29	7.8	7	12.0	1	16.0	..	....	42	10.0
Second period: Oct. 10 to Oct. 19	2	4.5	10	8.2	12	13.8	5	17.6	1	24.0	30	13.6
Third period: Oct. 20 to Oct. 29	..	...	1	9.0	3	14.0	3	18.3	8	25.2	15	16.6
Fourth period: Oct. 30 to Nov. 9	..	...	1	9.0	5	12.0	1	18.0	6	27.8	13	16.7
Fifth period: Nov. 10 to Dec. 26	1	4.0	8	7.3	4	12.0	3	18.0	4	24.2	20	13.1
Total and Aver.	8	4.3	49	8.2	31	12.8	13	17.5	19	25.3	120	14.0

## PATHOLOGIC ANATOMY

The necropsies were performed under ideal conditions, usually within a few hours, only rarely later than twelve hours after death. The tissues were routinely preserved in Zenker's fluid, occasionally in liquor formaldehydi. Fresh material was sometimes used for the study of cloudy swelling. Tissues routinely sectioned were heart, lungs, peribronchial lymph nodes, spleen, suprarenal, kidney, liver and brain. As occasion demanded sections were taken from skin, subcutaneous tissues, muscles, aorta and vessels in general, thoracic duct, extrapulmonary bronchi, semilunar ganglia, ureter, prostate, bladder, testes,

tongue, tonsils, intestines, pancreas, mesenteric lymph nodes, pituitary gland and spinal cord. The stain used for the accompanying photomicrographs was the eosinmethylen blue combination.

The description of the structures will be given in the order in which they are usually examined here at the necropsy (modified Zenker-Letulle method).

*External Appearance.*—The average age was 25.21 years; the average weight 76 kg.; the average height 174 cm. No great variations from these figures occurred. Emaciation was observed only in the more protracted cases. The postmortem lividity was generally most extensive. The face as well as almost the entire body was of a dusky color, sometimes even purplish black. In about two-thirds of the cases a bloody, sometimes frothy discharge exuded from the nostrils and from the mouth. There was no marked variation from the standard of cadaveric rigidity, but there seemed to be a tendency for it to be somewhat delayed. The superficial glands were never found palpably enlarged. Edema, although always looked for, was never present, and this should be emphasized in view of considerable kidney changes to be described below. The joints were never enlarged, nor was any arthritic condition demonstrated at necropsy, although it was sometimes seen clinically.

The chest was frequently considerably expanded, often unequally, This is no doubt due to the marked compensatory inflation of the lung and the pleuritic effusions. Scaphoid abdomen has been described (Kuskow<sup>2</sup>). This is probably coincidental and did not occur here, excepting in isolated cases.

*Skin.*—Various skin lesions have been described. Of these, the ones mentioned most frequently are exanthemata, resembling measles or scarlet fever; diffuse redness of the skin; sudamina and miliaria (Kuskow,<sup>2</sup> Leichtenstern<sup>1</sup>). Miliaria was very frequent and due to the profuse sweating (grippe sudorale). Such conditions as urticaria and psoriasis mentioned in connection with influenza are probably coincidental. In our series two cutaneous lesions occurred in a large number of cases. In about 20 per cent. of our patients there were multiple petechial hemorrhages in the form of minute, dusky, blue black areas, varying in diameter from 1 to 3 mm., and being most frequently met with in the axilla and over the scapula, although occasionally seen elsewhere. Because of the intense postmortem lividity they were recognized with difficulty. Microscopically (Fig. 1), small hemorrhages (up to the size of a low power microscopic field), were seen in the papillary layer of the skin, a papillary projection being often entirely flooded with red cells and only occasionally were these

hemorrhages seen in the deeper layers. These extremely superficial hemorrhages may be looked on as resembling the purpura hemorrhagica of influenza (Pick,<sup>7</sup> Drasche,<sup>8</sup> etc.).

The other skin lesions occurred in the form of small, discrete, slightly raised, red papules or vesicles with slightly turbid but rarely frankly purulent contents, in about 60 per cent. of this series. This condition was almost entirely confined to the sternal region. Microscopically, the sebaceous glands were hugely dilated and heavily infiltrated with polymorphonuclear cells; frequently they were entirely destroyed and replaced by a necrotic mass or a small abscess. Besides the polymorphonuclear cells, small round cells, with occasional plasma cells could be seen. The sweat glands were seldom involved. This condition did not seem to resemble acne nor the several forms of erythema multiforme described in relation to influenza (Krannhals,<sup>9</sup> Kuskow,<sup>2</sup> etc.). This we regard as a toxic necrosis of the sebaceous glands, produced, perhaps, by endothelial proliferation of its vessels, and analogous to the toxic acnitis of tuberculosis. Its characteristic site, over the sternal region, renders it unlikely that we are dealing with a simple acne.

In about 10 per cent. of our series jaundice was present. This was never very marked, and amounted to little more than a tinging of the sclera and skin. Blanton and Irons<sup>10</sup> found it nine times in 123 post-mortems; the majority of these cases appeared late in the epidemic. Symmers<sup>11</sup> saw it in seven out of twenty necropsies.

*Subcutaneous Tissues.*—Kuskow mentions no general changes, but in most of our cases the tissue was grossly somewhat more moist and congested than normal. Microscopically, nothing further was noted. In three necropsies, and in another not included here, a generalized subcutaneous emphysema was present. No mention of this complication is made in the voluminous European literature on the preceding pandemic, and during the present it appears to have appeared but rarely. In this camp, including all the clinical cases, it occurred nine times, the incidence, therefore, being 0.07 per cent. It was always most pronounced over the upper anterior chest, the neck and the lower part of the face, but in several cases it was distributed over the entire body; in one instance the left side of the scrotum was hugely ballooned.

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7. Pick: Ueber Influenza, Verhandl. d. 22 Cong. f. inn. med., Wiesbaden, 1905.

8. Drasche: Influenza, Wien. med. Wchnschr., Nos. 10, 12, 17, 1890.

9. Krannhals, H.: Die Influenzaepidemie des Winters 1889-90 in Riga, St. Petersburg, 1891.

10. Blanton, Wyndham B., and Irons, E. E.: A Recent Epidemic of Acute Respiratory Infection at Camp Custer, Mich., J. A. M. A. **71**:1988 (Dec. 14) 1918.

11. Symmers, Douglas: Pathologic Similarity Between Pneumonia of Bubonic Plague and of Pandemic Influenza, J. A. M. A. **71**:1482 (Nov. 2) 1918.

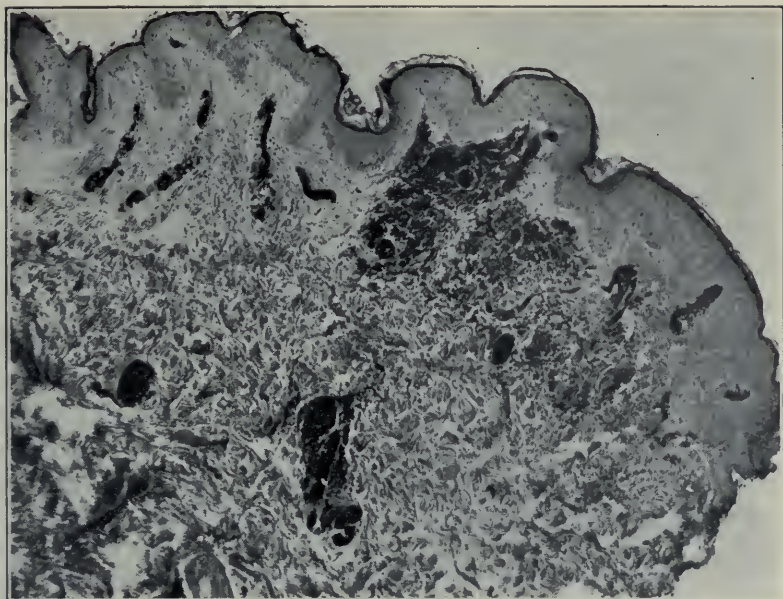


Fig. 1.—(Skin over upper chest.) Purpura hemorrhagica. Note dense hemorrhages in papillary layer of derma.



Fig. 2.—(Skin over chest.) Acute toxic necrosis of sebaceous gland. Note huge dilatation, cellular infiltration and necrosis.

The subcutaneous tissue appeared as if innumerable air bubbles were scattered throughout. The condition is being described in a separate communication where the details and the literature of the subject are given (Meyer and Lucke<sup>12</sup>). We need only say here that we found neither gross nor microscopic changes in the various organs which differed in any way from those of the rest of this series, with the exception that acute ulcerative bronchiectasis was more frequently noted here. We believe that the air escaping through the eroded bronchial wall was forced into the loose peribronchial areolar tissue and thence by line of least resistance gained the mediastinum and the subcutaneous tissue.

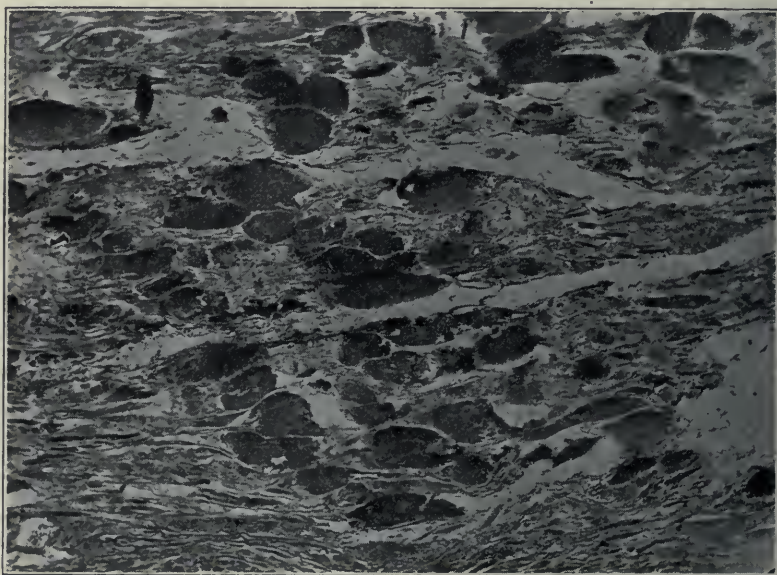


Fig. 3.—(Rectus muscle.) Coagulation necrosis (Zenker's hyaline degeneration), and early regeneration. Note swollen, evenly staining fibers, devoid of striations. In places clumps of nuclei denoting early regeneration may be seen.

*Muscles.*—In three instances considerable portions of the recti were of smooth, light reddish brown color, and had a peculiar, translucent appearance; in several more cases, about ten similar but smaller areas could be seen. This condition was confined to the abdominal muscles. Microscopically, typical Zenker's coagulation necrosis was met with (Fig. 3). This sometimes was present in only isolated fibers, but, in the three cases mentioned, extended over large areas. In one instance

12. Meyer, Jacob, and Lucke, Baldwin: Subcutaneous Emphysema, a Complication of Influenza, in Publication.

a marked acute myositis, with areas of necrosis and peripheral regeneration, was seen. Here dense masses of fibrin penetrated between the muscle fibers and into the structureless necrotic mass. Large numbers of round cells, polymorphonuclear cells and aggregations of muscle nuclei, in bundles and rows, were seen, especially at the periphery of the necrosed area (Fig. 4). Abscesses occurred in only one of this series, and in another instance among the cases of chronic influenza, although in the surgical wards, six abscesses of the rectus muscle were treated as complications of influenza. Rupture of the

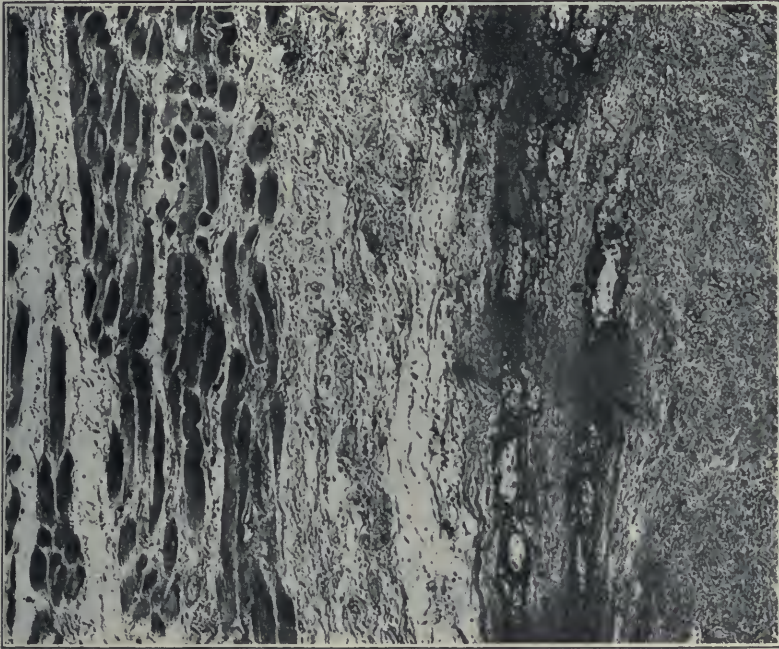


Fig. 4.—(Rectus muscle.) Acute suppurative myositis. Note partial necrosis, cellular infiltration and large amount of fibrin (right side of photograph).

rectus muscle and hemorrhagic exudations have been reported occasionally, but it did not occur in this series, although we have found it in noninfluenzal infections. Kuskow,<sup>2</sup> who saw several such hemorrhagic exudations in the muscles of the thorax and in the recti, believed it to be due to changes in the capillary walls, but also discusses the possibility of it being due to changes in the sympathetic nervous system. During the present European epidemic changes in the muscles seem to have occurred in from 10 to 20 per cent. of the cases (British Commission<sup>3</sup>). It must be said that the two most pronounced instances

of coagulation necrosis were present in conjunction with subcutaneous emphysema; this, however, is probably coincidental.

*General Internal Inspection.*—We mention here only in a general way the site of the abdominal organs, since this may be of some clinical interest. Usually the liver and the lower pole of the spleen extended well beyond the costal margins, due not only to a general increase in the size of these organs, but also to accumulations of pleural fluid, pressing them downward. The details of this and the external appearance of the other organs will be given under their respective headings.

TABLE 3.—LEUKOCYTE COUNTS IN A NUMBER OF FATAL CASES OF INFLUENZA

Necropsy Number	Duration of Disease, Days	Days before Death	Number of Leukocytes	Necropsy Number	Duration of Disease, Days	Days before Death	Number of Leukocytes
148	7	5	3,100	211	29	13	2,300
		3	2,100			7	8,700
		Day	3,900				
151	8	5	6,200	216	25	12	17,500
159	11	1	5,700	219	30	24	6,300
						?	10,000
160	12	9	10,200			14	13,600
		8	9,600				
		7	3,400	253	12	7	10,700
		5	8,600			6	10,100
						5	7,000
163	6	4	4,700			4	3,400
		3	7,800			3	3,800
		2	6,400			1	4,100
		1	8,000				
				258	29	9	11,100
165	8	3	7,000				
		2	12,200	262	45	30	8,400
		1	4,800			27	4,300
						24	11,000
170	15	7	4,300			17	10,000
		6	6,600				
		5	6,500	278	18	10	11,400
		4	8,400				
		3	11,000	280	24	4	17,600
						6	20,600
190	19	2	6,800				
				302	8	2	3,000
196	22	18	4,000				
		11	3,400	306	7	2	7,200
		6	10,000				
				316	11	6	4,300
201	24	17	4,000			4	6,400
		15	6,000			3	8,400
		14	3,600			2	9,700
		12	11,400				
		9	21,600	324	20	8	17,500
						3	20,200
206	28	6	5,000				

*Peritoneum.*—Peritonitis appears to be one of the rarest complications of influenza. Kuskow<sup>2</sup> collected the literature and found only eleven cases on record. Most of these coexisted with inflammations of other serous membranes, but some were thought to be primary by the writers. Blanton and Irons,<sup>10</sup> and Stone and Swift,<sup>13</sup> observed

13. Stone, Willard J., and Swift, George W.: Influenza and Influenzal Pneumonia at Fort Riley, Kan., J. A. M. A. 72:487 (Feb. 15) 1919.

one acute case of peritonitis in 123 and 55 necropsies, respectively. In our series it occurred in none of the acute, and three times in the chronic cases, associated in every instance with pleuritis, and undoubtedly secondary to the pleural complication. The rarity of this condition is in striking contrast to the frequency with which it occurred during the measles-streptococcic epidemic of the preceding year.

*The Blood Vascular System.*—Blood Vascular Changes in General: In order to avoid repetition, certain general changes are enumerated here. Details, as they affect various structures, will be given in their proper place.

Grossly, there was an extreme congestion of practically all the structures of the body, the cut surface generally being excessively bloody. This was especially noticeable in the heart, kidneys, liver and brain. Microscopically, congestion and hemorrhages constitute ever recurrent findings. The capillary endothelium was frequently considerably proliferated, and the lumen of even good sized arterioles and venules was occluded with smooth, homogeneous, hyaline thrombi, or densely packed conglutination thrombi, consisting of degenerating red cells. Klebs<sup>14</sup> was the first to call attention to this condition, and believed vascular changes to be the primary and most important changes in influenza, and the catarrhal and inflammatory processes to be sequels of occlusion of capillaries. He described these capillary thrombi as consisting of granular degeneration products of red and white cells, occasioned by flagellated monads. (The flagellated organisms of Klebs and certain protozoa found here will be discussed in the bacteriologic part of this paper.) The occlusion of the capillaries occasions hyperemia of the neighboring parts, inflammations and exudations, and the deposition of pathogenic organisms which find in the thrombotic tissue a favorable medium. Klebs believed the cerebral symptoms and other functional changes in the nervous system to be due to these circulatory disturbances. We may say here that various other observers have been unable to confirm Klebs' view as to the importance of the flagellated protozoa. It may be, however, that the toxins producing the thrombi act further on the various tissues and that a combination of the vascular changes and bacterial activity bring about the anatomic alterations encountered in influenza.

The hyaline and conglutination thrombi have been experimentally studied by Flexner,<sup>15</sup> Pearce,<sup>16</sup> Simonds,<sup>17</sup> and others. Throughout the

14. Klebs, E.: Zentralbl. f. Bakteriöl. u. Parasitenk. 7:145, 1890; Deutsch. med. Wchnschr., Nos. 14 u. 16, 1890.

15. Flexner, Simon: J. M. Res. 8:316, 1902.

16. Pearce, Richard: J. M. Res. 12:329, 1904.

17. Simonds, J. P.: The Formation of Agglutination Thrombi in the Livers of Dogs after Injection with Witte's Peptone, J. Infect. Dis. 24:297 (March) 1919.

tissues one frequently sees shadow erythrocytes denoting considerable blood destruction. The relative scarcity of polymorphonuclear leukocytes in the various tissues showing pathologic changes is striking, and gives one the impression that a myeloid intoxication exists here. A number of reports have given results of white blood counts and the consensus of opinion seems to be that a leukopenia is generally present. This occurred practically in all our clinical cases, and was looked on as one of our most important diagnostic aids. In Table 3 the counts of a number of the fatal cases are given. It will be seen that generally the leukopenia persisted throughout the disease, but that sometimes a slight leukocytosis occurred toward the end. In the

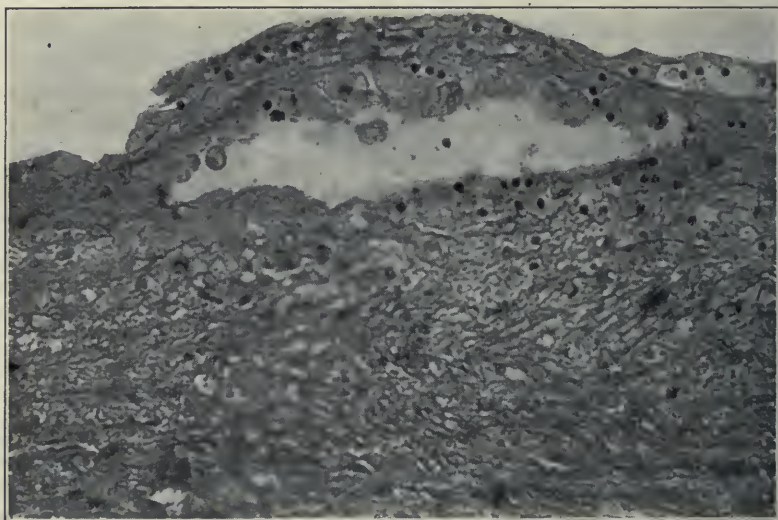


Fig. 5.—(Abdominal aorta.) Acute atheroma. Note slight bulging, cavitation and presence of huge, fatty degenerated cell. The most superficial layer of the intima is not affected.

cases where leukocytosis was present throughout, the pneumonic complications were of the croupous lobar type, or an associated purulent meningitis existed.

*Aorta, Thoracic Duct and Vena Cava.*—Definite subintimal changes, commonly looked on as the earliest manifestation of arteriosclerosis, were found in ninety-eight of a total of 120 cases in which a note was made on the condition of this vessel. The changes appeared as opaque, pale yellowish, or light orange yellow, narrow, firm streaks and corrugated ridges, generally occurring longitudinally on the posterior wall. The term "willow-tree branches," which has been applied to this condition, aptly describes it. Only exceptionally were hyaline plaques

found. The elasticity was never impaired, as tested in instances by a stretching apparatus. Generally, the entire length of the vessels presented these changes, but sometimes they seemed more marked in the ascending arch than in the abdominal aorta. Microscopically (Fig. 5), the endothelium was not affected. The more superficial layers of the intima were generally somewhat loosely arranged. The deepest layer was fibrous and swollen. At what appears to be a later stage the swelling is more pronounced. Very large cells with a ragged, granular, vacuolated, disintegrating cytoplasm were seen. Their nuclei were variable in their staining affinities and were often entirely absent.

Small, ragged walled cavities, bounded by the muscular wall and the most superficial layer of the intima were met with commonly. These, no doubt, were sometimes due to the dropping out of the degenerated cells during the process of sectioning, but are likewise the product of fatty and granular degeneration. A few scattered, small, round cells were found, but no definite infiltration. This early atheroma has been described by one of us (Lucke<sup>18</sup>) as frequently occurring in necropsies of measles patients. Karsner<sup>19</sup> found such changes in sixty-two out of eighty-one soldiers dying from endocarditis, and so forth, following war wounds, and in a large percentage of patients dying of various acute infections in this camp, this early aortic change was met with. A more detailed study of this finding is in progress.

The only other condition worthy of note was a diffuse hemoglobin tinting of the aorta and other great vessels. This occurred in many instances, even at necropsies performed within a few hours after death, and is probably a manifestation of rapid blood destruction. A mention of this condition is made by Le Count.<sup>20</sup> The vena cava and the other large vessels presented no gross alterations.

The thoracic duct, in every instance, was of normal diameter, thin walled, with a slightly pink mucosa. Neither gross nor microscopic changes were noted.

*Pericardium.*—Pericarditis was met with seven times; twice sero-fibrinous, on three occasions fibrinous, once fibrinopurulent, and once frankly purulent. Microscopically, the usual fibrinopolynuclear exudate was found. In each instance an associated pleuritis was probably the starting point of the inflammation. In approximately 20 per cent. of this series the pericardial fluid amounted to 50 or 60 c.c.; this, how-

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18. Lucke, Baldwin: Postmortem Findings in Measles, Bronchopneumonia and Other Acute Infections, J. A. M. A. **70**:2006 (June 29) 1918.

19. Karsner, Howard T.: Acute Endocarditis Following War Wounds, Arch. Int. Med. **22**:296 (June) 1918.

20. LeCount, E. R.: The Pathological Anatomy of Influenzal Bronchopneumonia, J. A. M. A. **72**:650 (March 1) 1919.

ever, was most likely mechanical in origin, due to the pressure on the great veins by pleural exudate. Punctate, hemorrhagic extravasations were often seen over both the visceral and parietal pericardium, and in a majority of cases, definite hyperemia was present. Blanton and Irons<sup>10</sup> found serofibrinous pericarditis thrice in 123 necropsies; Kuskow,<sup>2</sup> five times in forty necropsies. From the literature (Kuskow<sup>2</sup>) it would seem that pericarditis is a rare complication of influenza, depending most likely on associated pleuritis.

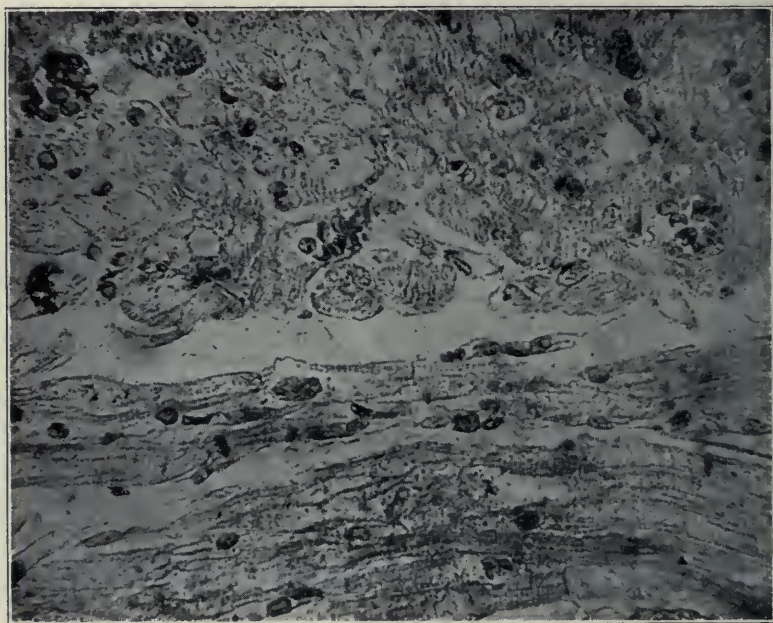


Fig. 6.—(Heart.) Cloudy swelling and vacuolization. Note vacuoles in body of muscle cells (upper half of photograph), swelling of fibers, large oval nuclei and occasional chromatolysis.

*Heart.*—Contradictory reports are given in the literature. Symmers,<sup>11</sup> in twenty necropsies, found right-sided dilatation, congestion of capillaries and exceptionally cloudy swelling. Nuzum<sup>21</sup> and his co-workers, in forty necropsies, found the right heart acutely dilated. Stone and Swift,<sup>13</sup> in fifty-five necropsies, found right-sided dilatation in thirty-one instances, and dilatation of both sides in seven instances, and observed definite parenchymatous changes in the myocardium in many instances. No histologic examinations, however, were recorded.

21. Nuzum, John W., Pilot, Isadore, Stengle, F. H., and Bonar, B. E.: Pandemic Influenza and Pneumonia in a Large Civil Hospital, *J. A. M. A.* **71**:1562 (Nov. 9) 1918.

Ribbert,<sup>22</sup> and Birch-Hirschfeld<sup>23</sup> found no anatomic alterations. Wallis<sup>24</sup> and Kuskow<sup>2</sup> found acute parenchymatous inflammations as in other infectious diseases. We strongly support the opinion of the latter that the heart is always more or less affected and presents always certain alterations. The weight of the heart was estimated in detail in sixty-six cases (Table 7). In 30 per cent. of these it was below 300 grams, with an average of 267 grams. In 60 per cent. it averaged 364 grams, and in 10 per cent. it weighed 400 grams with an average of 429 grams. On the whole, the heart weight appeared increased, due probably more to congestion and edema than to actual hypertrophy. Lyon<sup>6</sup> found 322 grams the average in his series of fifty-six cases. In 115 cases of our series the right heart presented more or less dilatation, and in a number of instances the left side was likewise relaxed. In eighty-nine cases an associated cloudy swelling was diagnosed grossly. In the majority of instances, then, we encountered parenchymatous changes analogous to those seen in other acute infections.

The heart muscle was usually flaccid, sometimes excessively so. The cut surface practically was always opaque, grayish red, with fine lines due to capillary congestion. The characteristic tigroid markings of fatty degeneration were never seen. Microscopic examinations were conducted on both fresh and fixed preparations. As a rule, a granularity obscuring striations and clearing on the addition of acetic acid was found. In the stained preparation these changes were less clear, but here (Fig. 6) also one would frequently see haziness or disappearance of the cross striations, and very frequently, small vacuolization. Here and there the nuclei were pale and irregularly stained; many being swollen, oval, granular and fragmented. All these changes are similar to those seen in diphtheria and typhoid fever. In the interstitial tissue, occasionally, a few wandering cells, or a granular debris, were found. The intermuscular spaces were sometimes broad and contained a precipitated, granular mass, probably edematous in origin. The capillaries were often distended to an extreme degree; but very rarely small hemorrhages were seen. Conglutination and hyaline thrombi, spoken of above, were often seen, but not with the same frequency as in some of the other organs.

The endocardium, in a few instances, presented subendothelial, petechial hemorrhages of slight extent. The valve leaflets were involved

22. Ribbert: Anatomische und Bakteriologische Beobachtungen über Influenza, *Deutsch. med. Wchnschr.*, No. 4, p. 15, 1890.

23. Birch-Hirschfeld: *Schmidt's Jahrb.*, **226**:111, 1890.

24. Wallis, C.: *Hygiea* **70**: 1890 (cit. *Schmidt's Jahrb.*, 1891).

only once, where acute vegetations were seen on the mitral valve. It would appear, from the literature, that endocarditis is one of the rare complications, and probably always secondary in origin.

*Respiratory System.*—Nares: The mucosa of the nares, especially in the cases early in the epidemic, was somewhat swollen, deep red and frequently exuded blood. No microscopic sections were made.

*Accessory Nasal Sinuses.*—These will be described here, rather than in the order of the necropsy. In sixty-five cases the accessory nasal sinuses were examined. In eight of them no gross alterations

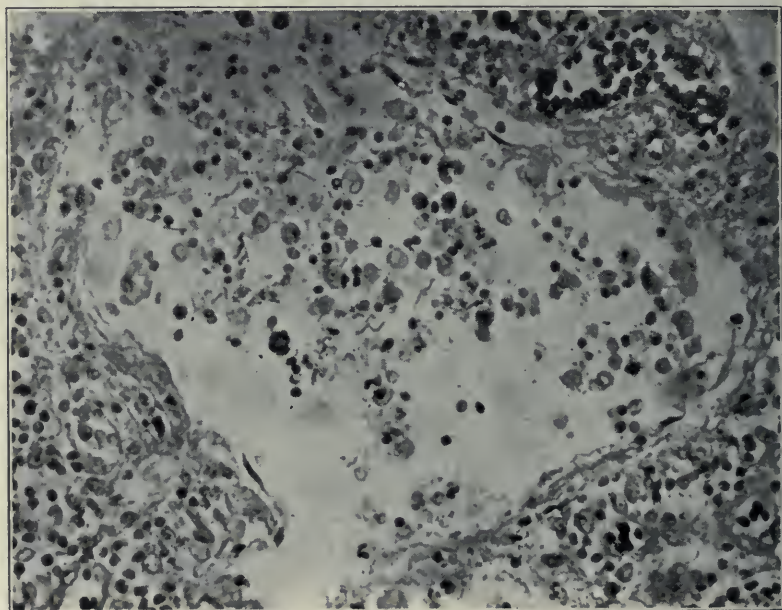


Fig. 7.—(Peribronchial lymph node.) Acute sinus catarrh. Note the widely distended lymph sinus and the presence of large mononuclear cells. The sinuses are generally more packed with cellular structures. This section was chosen to bring out the details.

were present. Generally, the mucosa was reddened, thickened, loose and the cavity contained a purulent or seropurulent material. Frequently this was heavily blood-stained, varying in consistency from a thin, watery, sanguineous exudate to a heavy, creamy, yellow, thick pus. The sphenoid sinus was involved fifty-one times, the ethmoid sinus forty-three times, the frontal sinus seventeen times, and the mastoid cells, on one or both sides, fourteen times. Stone and Swift,<sup>13</sup> in forty-one necropsies, found similar involvement in a large number of cases,

and Weichselbaum<sup>25</sup> and Drasche,<sup>8</sup> during the pandemic of 1889, saw similar changes. It would appear that the sphenoid sinus was the most frequently involved. Necrosis of the bone was never present, in marked contradistinction to the frequent and pronounced bone necrosis seen here during the measles outbreak of 1917-1918, even though at that time the accessory nasal sinuses were on the whole not so frequently affected as during the present pandemic.

*Peribronchial Lymph Nodes.*—In 115 cases congestion and edema of the peribronchial lymph nodes were grossly noted. In eleven cases no microscopic changes were demonstrable. The glands often attained

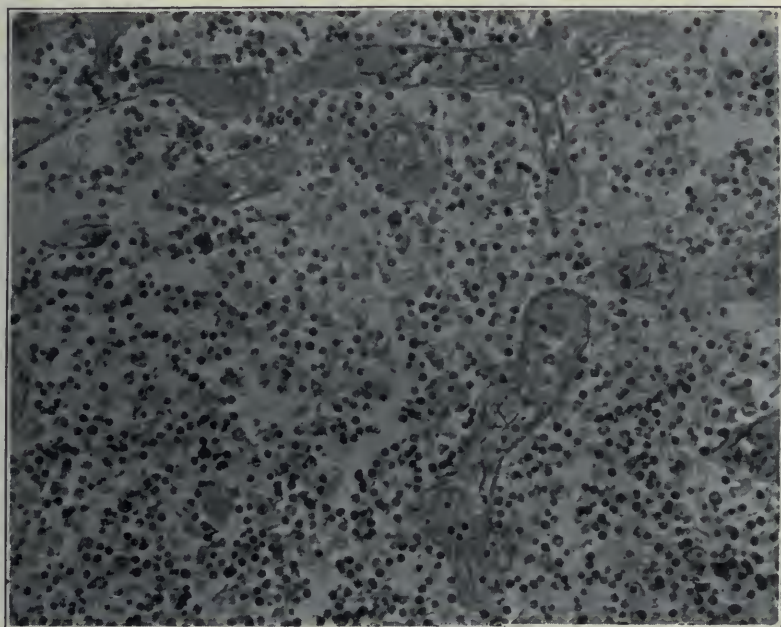


Fig. 8.—(Peribronchial lymph node.) Coagulation and fibrin thrombi. Note the densely packed and fused red cells, and strands of fibrin. Compare this with Figure 10 where the individual red cells are separate.

remarkable proportions, and it was not uncommon to see a mass the size of a walnut. Such excessive enlargement was present in thirty-two instances. The external appearance was generally a light reddish gray, occasionally a dark pinkish red. The consistency varied from mushy softness to flaccidity. The cut surface was practically always very moist, dripping blood stained fluid. The degree of congestion

25. Weichselbaum: Bakteriologische u. path.-anat. Untersuchungen über die Influenza u. Ihre Komplikationen, Wien. med. Wchnschr., No. 6, 1890.

varied, but the majority of cases were definitely congested, and, in some, tiny hemorrhages visible to the naked eye occurred. Microscopically, the lymph sinuses were widely distended and often packed with very large mononuclear, pale staining, phagocytic cells, containing bacteria and cell remnants (Fig. 7). Other sinuses showed a granular debris with delicate threads of fibrin, and, in some, dense accumulations of red cells were intermingled with the other constituents. Many cells resembled the phagocytic epithelial cells of the lung exudate. A number of camera lucida drawings of these cells made from both sources were compared and it seemed very probable that they belonged to the same group of elements. The lymphoid

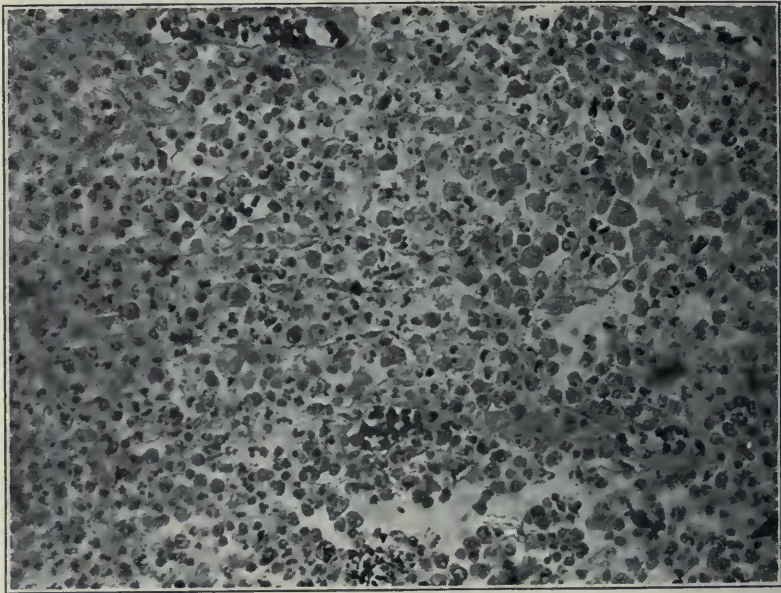


Fig. 9.—(Peribronchial lymph node.) Acute suppurative lymphadenitis. Note large numbers of polynuclear leukocytes throughout tissue. Note also the large mononuclear cells within the lymph sinuses and compare this with Figure 7.

tissue was generally loosely arranged, sometimes intermingled with a fine precipitate and occasionally fibrin. An active proliferation, as indicated by great numbers of large cells of the lymphoid type, appeared to be going on. Plasma cells occurred in considerable numbers in cases where the disease had persisted for some time.

The vessels throughout the glands were enormously congested, and now and then hemorrhagic foci were encountered. Almost in every instance some of the vessels contained smooth hyaline or conglutination, and, in a few cases, fibrin thrombi (Fig. 8). The vascular endo-

thelium was considerably swollen, the nuclei being often very large and the cytoplasm protruding into the lumen of the vessel. We believe that it is justifiable to look on the phagocytic cells in the lymph sinuses as of mixed origin. Part of them appear to be derivatives of vascular endothelium corresponding to the endothelial leukocytes that Mallory<sup>26</sup> has described. Others are probably epithelial, being carried to the lymph sinuses from the lung. These latter are differentiated by poorer staining, frequent vacuolization and other evidences of degeneration. On the whole, bacterial phagocytosis in the lymph node was rare. The perivascular spaces were packed with cells similar to those described, the relative absence of polynuclear elements being striking. In fact,

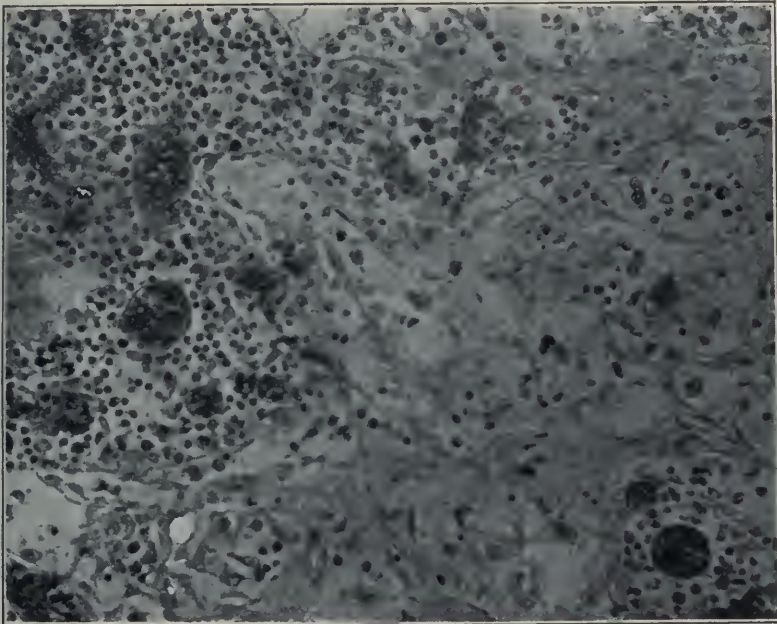


Fig. 10.—(Peribronchial lymph node.) Subacute productive lymphadenitis. Note the loosely arranged cellular young connective tissue. These changes are indicative of the fibrosis ultimately resulting.

these latter occurred only when the adjacent lung surface was covered with fibrinocellular exudate (Fig. 9). Now and then eosinophils, in inconspicuous numbers, were encountered. Occasionally the reticular fibrous tissue was actively proliferating, and large numbers of loosely arranged young connective tissue cells could be seen throughout the section. This subacute productive lymphadenitis occurred mainly in

26. Mallory, Frank B.: *Principles of Pathologic Histology*, Philadelphia, W. B. Saunders Co., 1914.

cases of some duration and appears to indicate the end-result of the process (Fig. 10).

To summarize the changes in the lymphatic glands: marked congestion and edema, acute sinus catarrh, frequent hyaline and conglutination thrombosis, and relative scarcity of polynuclear cells. Grossly, such changes have been described by Blanton and Irons,<sup>10</sup> Symmers,<sup>11</sup> Nuzum,<sup>21</sup> and others. Oberndorfer<sup>27</sup> examined some histologically and found enormous congestion, hemorrhages and proliferation of the endothelium, especially in the axillary glands.

*Larynx.*—The mucosa of the larynx was definitely reddened and somewhat swollen in only about one-third of our cases. Occasionally the glottis and surrounding structures were edematous, but ulcerations were never encountered. In a general way, the laryngeal mucosa was never as much involved as that of the lower trachea or the bronchi. This agrees with the observation of Drasche<sup>8</sup> and Oberndorfer. Leichtenstern describes several cases of hemorrhagic laryngitis, and B. Fraenkel<sup>28</sup> observed a laryngitis, with marked swelling and various degrees of redness, several times in association with a croupous exudate in thirty-three instances in his series of forty-five cases.

*Trachea and Bronchi.*—The mucosa of the trachea and principal bronchi was generally markedly reddened, cloudy and swollen, at other times it was of a paler red color and overlaid with mucopurulent or purulent secretions. The changes may be summarized as follows: The tracheitis and bronchitis were hemorrhagic in character sixty-three times, catarrhal thirty-one times, purulent twenty-three times, while in nine cases no gross alterations were noted. Hemorrhagic types were chiefly met in the more acute cases, the catarrhal and purulent forms occurring usually at later stages. Fibrinous exudates now and then covered a part of the tracheal or bronchial walls, but there were no distinct macroscopic ulcerations. Leichtenstern<sup>1</sup> believed that the inflammation was often most pronounced at the bifurcation, but this we cannot confirm. The contents of the tubes consisted usually of large amounts of frothy, blood stained material in the hemorrhagic types, while in the catarrhal and purulent forms great quantities of mucus, or thick yellow, purulent fluid were found.

Several writers have drawn attention to the uneven distribution of the bronchial inflammation, considering this as one of the important complications of influenzal bronchitis (Kuskow,<sup>2</sup> Leichtenstern,<sup>1</sup> etc.). We can agree with their statements, for in our cases the alterations

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27. Oberndorfer: Ueber die Pathologische anatomie der Influenza-artigen Epidemie, München. med. Wchnschr. 65:810, 1918.

28. Fraenkel, B.: Deutsch. Wchnschr., No. 28, 1890.

were usually not uniform. Thus, the bronchi leading to diseased parts were usually more affected than those supplying healthy lung tissue. On the other hand, we have occasionally seen bronchial tubes intensely inflamed, while no marked changes in the surrounding lung tissue existed. The small bronchial branches presented generally the same changes as the larger tubes. Microscopically, most pronounced alterations were observed. Of these, desquamative bronchiolitis was the most frequent, the mucosa here being almost entirely destroyed. Ulcerative bronchiolitis was also very common. Sometimes the entire bronchial wall was eroded and replaced by a densely necrotic mass

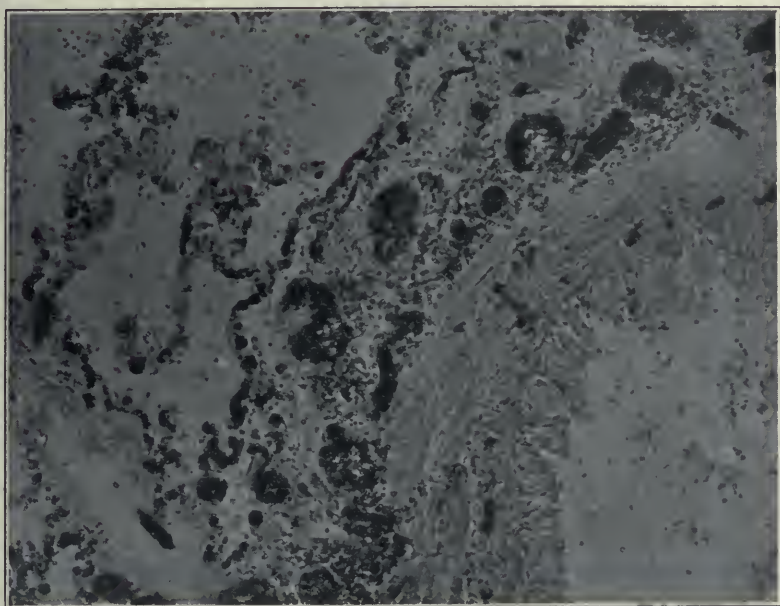


Fig. 11.—(Bronchus.) Acute hemorrhagic bronchitis. Note the dense congestion and small hemorrhages throughout the bronchial wall. The mucosa is partly necrotic but not as yet desquamated.

containing strands of fibrin and polymorphonuclear cells in various stages of degeneration. In the less affected bronchioles, and in the larger bronchial branches, extreme congestion and submucous hemorrhages were very general (Fig. 11). Thrombi of various natures, but usually hyalin, were common. The endothelium was often actively proliferated. Infiltration of the bronchial walls with polynuclear cells was frequent. The mucous glands usually presented mucoid degeneration. Bronchiectasis was relatively uncommon. Large ulcerations occurred in four instances only. This has been referred to above in connection with subcutaneous emphysema.

*Pleurae*.—The existence of pleuritis has varied greatly at different times and places. Thus, Symmers<sup>11</sup> emphasizes its infrequency, encountering it only thrice in twenty necropsies. Blanton and Irons,<sup>10</sup> in eighty of 123 necropsies; Hall, Stone and Simpson,<sup>29</sup> ten times in thirteen necropsies; Stone and Swift,<sup>18</sup> in thirty-one out of fifty-five necropsies; Nuzum and others,<sup>21</sup> practically always in forty necropsies. The majority of the above found it to be serofibrinous, and some lay stress on its serosanguineous character and its low fibrin content. During the preceding epidemic European writers found a similar discrepancy. Thus, Leichtenstern<sup>1</sup> saw seropurulent involvement twice in forty necropsies; Kundrat,<sup>30</sup> nine times in 126 necropsies; Mason,<sup>31</sup> in six of twenty-eight necropsies; Kelsch and Antony,<sup>32</sup> in nineteen out of 278 necropsies.

On the whole, the pleural involvement seems to have been less in the European pandemic of 1889 and succeeding years than in the present visitation. The discrepancy in the findings is probably not only due to the organism predominating in the various localities, but also to the period in an epidemic when the observations were made. Thus, our early cases presented far less pleural involvement than those occurring later in the epidemic. In each instance an associated pneumonitis was present. Primary pleuritis was never observed, although Kundrat emphasizes as one of the characteristics of influenzal bronchitis that it often leads to purulent pleuritis without accompanying pneumonia. It would appear, however, that no detailed microscopic studies were made by him or other writers who describe such a condition, and that their statements were based on macroscopic rather than on microscopic evidence.

In our series the pleura was involved on one or both sides in ninety cases. The exudate was sanguineous in twelve, fibrinous in twenty-seven, serofibrinous in nineteen, serofibrinopurulent in twenty-three, and frankly purulent in nine instances. The left pleura was somewhat more frequently involved than the right, the difference being as follows:

Exudate	Left Pleura	Right Pleura
Serosanguineous .....	6	8
Fibrinous .....	27	22
Serofibrinous .....	19	12
Seropurulent .....	21	19
Purulent .....	4	6

29. Hall, J. N., Stone, Murray, C., and Simpson, John C.: The Epidemic of Pneumonia Following Influenza at Camp Logan, Texas, *J. A. M. A.* **71**:1987 (Dec. 13) 1918.

30. Kundrat: *Wien. klin. Wchnschr.*, 1890.

31. Mason: *Boston M. & S. J.*, February, 1890.

32. Kelsch et Antony: *La Grippe dans l'armée Française en 1889-1890. Arch. de méd. et de pharm. milit.*, Paris **18**:1891. Kelsch: *Traité des Maladies Epidémiques. Tome III.* Paris, 1910.

It must be remembered that occasionally only one pleura was affected, and that, therefore, these figures differ from the consolidated incidence given above. The exudate was generally thin and apparently low in fibrin content. In the early part of the epidemic the sero-sanguineous types occurred most frequently, the fluid being definitely blood-tinged. Under fibrinous pleuritis are included all degrees of fibrinous exudation. Generally, only a small, fine, grayish, patchy deposit, often not more than a roughening of the pleura, was present. In the serofibrinous exudates small clumps of fibrin were floating in a relatively clear or only slightly turbid fluid. By serofibrinopurulent exudates are understood those fluids which were more definitely turbid. The purulent exudates were of the usual type. Analysis as to the amount of fluid could be made in seventy-one instances. The figures given apply to the fluid in either cavity. Thus, if both the right and left cavities contained a varying amount they were considered separately. Fluid was less than 100 c.c. in ten, between 100 and 500 c.c. in thirty-eight, between 500 and 1,000 c.c. in fifteen, between 1,000 and 2,000 c.c. in seven, and over 2,000 c.c. in one instance; the greatest number, therefore, containing less than 500 c.c.

Analysis in reference to the duration of the disease and period of the epidemic reveals the fact that the purulent and more pronouncedly fibrinous fluids occurred at a later stage of the disease or epidemic. Petechial hemorrhages were observed frequently, varying in extent, sometimes involving considerable areas and being in 50 per cent. associated with a pleuritis. Cytologically, the pleural exudate consisted chiefly of large mononuclear cells, with considerable numbers of polynuclear elements. Phagocytosis of bacteria was common. Microscopically, the pleura presented the usual changes encountered in exudative inflammations. The subserous vessels were generally hyperemic and frequently contained hyaline or conglutination thrombi.

*Lungs.*—The anatomic alterations of the lungs are usually the most pronounced and most striking. The question whether influenza is always accompanied by pneumonitis, or whether it is only one of the complications of this disease, has been much discussed, pro and con. Certainly, no matter what changes are present in the rest of the organs, pneumonic involvement is also encountered in the vast majority of instances. The widespread influenzal bronchitis prepares areas of lessened resistance for the secondary micro-organisms of the mouth and throat, which, in suitable environment, readily take on pathogenic properties and produce pneumonitis. It is this almost constant presence of a number of different organisms, each having its own special characteristics and producing its own special changes, which has led to the wide discrepancy in the reports of the anatomic changes. This is

perhaps more true of the lungs than of any other organ. It must always be remembered that the changes encountered are usually due to various secondary invaders of an already pathologic field, and while we shall attempt below to describe the alterations occurring in the lungs from which only one type of organisms was isolated, it seems best to first present the picture, regardless of the micro-organisms found in culture, for it is hardly possible to decide the exact extent for which this or that micro-organism was responsible. At all events it has been our impression that the chief characteristic of influenzal pneumonitis lies in the multiformity of lesions. Quotations from the literature have been especially limited here because of lack of space, but a very brief review is deemed necessary.

TABLE 4.—DURATION OF INFLUENZAL PNEUMONITIS IN RELATION TO DURATION OF DISEASE

Days Sick with Influenza	Duration of Pneumonia								Total Number of Cases	Average Duration in Days		
	1 to 5 Days		6 to 10 Days		11 to 15 Days		16 to 20 Days				More than 20 Days	
	No. of Cases	Average Duration in Days	No. of Cases	Average Duration in Days	No. of Cases	Average Duration in Days	No. of Cases	Average Duration in Days			No. of Cases	Average Duration in Days
1- 5.....	8	2.75	....	.....	....	.....	....	.....	....	.....	8	2.75
6-10.....	29	3.79	14	6.66	....	.....	....	.....	....	.....	43	5.33
11-15.....	6	3.67	20	8.20	5	13.20	....	.....	....	.....	21	8.36
16-20.....	2	4.50	2	8.00	6	12.00	2	17.00	....	.....	12	10.33
Over 20.....	....	.....	1	9.00	3	14.00	8	17.63	3	26.00	15	16.66
Total and Aver.	45	3.68	37	8.02	14	13.07	10	17.32	3	26.00	109	

The usual form of influenzal pneumonitis has been described as lobular, the consolidations varying in size from very minute areas to entire lobes, and occurring almost as frequently in the upper as in the lower lobes. Such types have been described by Kelch and Antony,<sup>22</sup> Wallis,<sup>24</sup> Marchand,<sup>33</sup> Ribbert,<sup>22</sup> Kundrat,<sup>30</sup> Kuskow,<sup>2</sup> Drasche<sup>8</sup> and others. All of these authors describe the foci more or less differently. Thus, the cut surface was sometimes found smooth, at other times granular. The periphery was rarely sharply demarcated. The lung tissue was generally hyperemic, but sometimes it appears to have been definitely anemic. Consistency and color of these consolidated areas has varied so greatly that details cannot possibly be given. Purulent pneumonitis has been observed by Krannhals,<sup>9</sup> Kuskow,<sup>2</sup> Kundrat,<sup>30</sup> Drasche,<sup>8</sup> etc. Gangrene of the lung tissue has been found associated

33. Marchand: *Berl. klin. Wchnschr.*, No. 33, 1890.

with this suppurative pneumonia, and has occasionally been found independently (Marchand,<sup>33</sup> Drasche,<sup>8</sup> A. Fraenkel,<sup>34</sup> Kundrat,<sup>30</sup> Kuskow<sup>2</sup>). Indurative pneumonitis has been observed by Drasche<sup>8</sup> and Kundrat.<sup>30</sup> True lobar pneumonia of the croupous type seems to have occurred with greater frequency during and after influenza than usually (Sokolowski,<sup>35</sup> Kundrat,<sup>30</sup> etc.). Noncroupous lobar pneumonia, or pseudolobar lobular pneumonia, has been so frequently encountered that it seems to be almost characteristic of this disease. The consolidated tissue here has an even, smooth cut surface and presents under the microscope an exudate, poor in fibrin and rich in catarrhal and polymorphonuclear cells (Gaescher,<sup>36</sup> Marchand,<sup>33</sup> L. Frank,<sup>37</sup> R. Simon,<sup>38</sup> etc.).

Microscopically, the exudate in the various forms has been found of every conceivable composition. Pfeiffer<sup>39</sup> found fibrin totally absent, or present only in small amounts. The cells were generally catarrhal or polymorphonuclear with frequent infiltration of the alveolar walls. He believed that influenzal pneumonia manifested itself first by peribronchial inflammation, which by coalescence formed larger lobar consolidations. Ribbert<sup>22</sup> found fibrin to vary greatly in amount, the cells being chiefly polymorphonuclears and desquamated epithelium with many red cells. Klebs<sup>14</sup> found fibrin constantly present and large numbers of red cells; polymorphonuclear leukocytes being later invaders. Ziegler<sup>40</sup> likewise emphasized the hemorrhagic character. Kundrat,<sup>30</sup> Sahli<sup>41</sup> and Birch-Hirschfeld<sup>23</sup> found the exudates very fibrinous and often hemorrhagic. Kuskow<sup>2</sup> found fibrin in varying amounts, generally present but seldom in large quantities. The exudate was often frankly hemorrhagic, usually catarrhal cells predominated, but sometimes the pneumonitis was frankly purulent. Leichtenstern<sup>1</sup> observed most frequently mixed catarrhal and fibrinous exudates. Finkler,<sup>42</sup> in whose cases streptococci were the most frequent invaders, found an acute interstitial pneumonia with catarrhal exudation in the alveolar septums and air sacs, and only a slight amount of fibrin. He compared the lesions with the changes seen in erysipelas.

34. Fraenkel, A.: *Deutsch. med. Wchnschr.*, p. 432, 1892.

35. Sokolowski: *Schmidt's Jahrb.* **228**:149, 1890.

36. Gaucher: *Bull. Soc. méd. des hôp.*, 1890.

37. Frank, L.: *Schmidt's Jahrb.* **233**: 1890.

38. Simon, R.: *Brit. M. J.*, 1892.

39. Pfeiffer, R.: *Deutsch. med. Wchnschr.*, Nos. 2 u. 21, 1892; *Ztschr. f. Hygiene* **13**: 1893.

40. Ziegler: Quoted by Leichtenstern.

41. Sahli: Quoted by Leichtenstern.

42. Finkler, B.: *Die Ak. Lungen entzündungen als Infections Krankheiten*, Bonn, 1891. Also *Deutsch. med. Wchnschr.*, No. 5, 1890.

During the present epidemic the pneumonitis was chiefly lobular. Symmers<sup>11</sup> found the exudate hemorrhagic, purulent and catarrhal with fibrin absent. Blanton and Irons<sup>10</sup> report the exudate fibrinous only once, and Opie<sup>5</sup> and his co-workers describe suppurative pneumonitis. Oberndorfer<sup>27</sup> found marked hemorrhagic infiltration, and, in the later stages, catarrhal and suppurative exudations. Chickering and Park<sup>43</sup> describe a staphylococcus pneumonia characterized by innumerable abscesses in the lung. Macallum<sup>44</sup> found the exudate to vary with the organisms present.

All the above indicates that according to time and place the disease changes have varied considerably.

TABLE 5.—EXTENT OF LUNG INVOLVEMENT IN RELATION TO DURATION OF DISEASE

Number of Lobes Involved	Duration of Disease			Total
	1 to 10 Days	11 to 20 Days	20 Days	
1	2 cases	4 cases	3 cases	9 cases
2	7 cases	3 cases	7 cases	17 cases
3	7 cases	8 cases	4 cases	19 cases
4	15 cases	19 cases	3 cases	37 cases
5	26 cases	11 cases	5 cases	42 cases

TABLE 6.—DISTRIBUTION AND CHARACTER OF BRONCHOPNEUMONIA

	Left Lung	Right Lung
Patchy Bronchopneumonia:		
Upper lobe .....	47	45
Middle lobe .....	..	38
Lower lobe .....	46	43
Confluent Bronchopneumonia:		
Upper lobe .....	35	37
Middle lobe .....	..	28
Lower lobe .....	55	56

The duration of the pneumonitis was estimated from the day that lung involvement was first observed to day of death (Table 4). Such an estimation is only accurate in a relative way, but certain interesting features were brought out thereby. It shows that eight of the 109 cases developed pneumonia within the first five days of the disease, and forty-three more within the first ten days, so that about half of the entire series presented lung involvement relatively early in the attack. The other half showed definite pneumonitis considerably later, fifteen cases developing it after the disease had persisted for twenty

43. Chickering, H. T., and Park, James H.: Staphylococcus aureus Pneumonia, J. A. M. A. **72**:617 (March 1) 1919.

44. MacCallum, W. G.: Pathology of Influenza Following Pneumonia, J. A. M. A. **72**:720 (March 8) 1919.

days. Once the pneumonitis was established it proved fatal within a relatively short time. Thus, in forty-five instances, the duration was 3.68 days, in thirty-seven it was 8.02 days, while in only three cases did the pneumonic process persist over twenty days, giving an average of twenty-six days. Further details are shown in the table. Pneumonitis occurred in 124 instances, in two cases none was present. In both of these a rapidly fatal epidemic meningitis occurred.

TABLE 7.—WEIGHTS AND MEASUREMENTS OF PRINCIPAL ORGANS  
Average age: 25.21 years. Average weight: 76 kg. Average height: 174.8 cm.

Organ	No. of Cases	Range of Weights in Gm.	No.	Per Cent. of No. Examined	Average Weight in Gm.	Average Size in Cm.		
						Length	Width	Thickness
Brain.....	46	Below 1,400	18	39.1	1,300			
		1,400 - 1,600	23	50.0	1,452			
		Over 1,600	5	10.9	1,739			
Heart.....	66	Below 299	20	30.3	267			
		300 - 399	39	59.1	364.3			
		Over 400	7	10.6	429.3			
Left lung.....	65	Below 500	10	15.3	392.5			
		500 - 999	44	67.7	717.1			
		Over 1,000	11	16.9	1,328.6			
Right lung.....	64	Below 500	6	9.4	392.5			
		500 - 999	35	54.7	761.12			
		Over 1,000	23	35.9	1,343			
Spleen.....	68	Below 150	10	14.7	127.2	12.0	7.6	2.9
		150 - 249	31	45.6	192.9	13.6	8.4	3.5
		250 - 449	25	36.8	321	15.5	9.7	4.1
		Over 450	2	2.9	590	18.7	12.0	5.0
Left kidney....	50	Below 150	5	10.0	135.4	11.1	6.0	3.25
		150 - 299	43	86.0	202.75	12.5	8.08	3.3
		Over 300	2	4.0	310	13.0	6.5	5.5
Right kidney...	50	Below 150	5	10.0	135.8	11.0	5.9	3.2
		150 - 299	44	88.0	207.7	12.15	5.8	3.72
		Over 300	1	2.0	310	13.0	6.5	6.0
Liver.....	61	Below 1,500	4	6.6	1,248.75	25.5	15.5	7.9
		1,500 - 1,999	29	47.5	1,829.3	28.3	20.17	7.8
		Over 2,000	28	45.9	2,254.5	29.25	21.2	8.28

The amount of lung involvement in relation to duration of disease is shown in Table 5. This table shows that usually the involvement was extensive, since in 98 cases three or more lobes presented areas of consolidation. Both lungs were involved in 116 cases, the right lung alone in three, the left alone in five instances.

The weights of the lungs were estimated in sixty-five instances, details of which are shown in Table 7. In only a small per cent. relatively was the weight of either lung below 500 grams. In 67 per cent. of the cases the left lung averaged 717 grams; in 55 per cent. the right lung averaged 761 grams, in 17 per cent. the left lung averaged 1,328 grams, and in 36 per cent. the right lung averaged 1,343 grams. The lungs are, therefore, considerably heavier than in the average case

of bronchopneumonia, especially that of the aged. LeCount,<sup>20</sup> comparing the lung weight of influenzal pneumonia with that of croupous pneumonia, found the ratio of lung weight to body weight similar in these diseases. The anterior edges of the lungs were generally inflated, the compensatory emphysema being often very marked. Only in a relatively small number of instances were air bladders or distended, pearl-like, ruptured air vesicles seen. The posterior borders were usually the site of involvement, and had a slatey blue to reddish purple color. The upper lobes were almost as frequently attacked as the basal lobes, which seems one of the characteristics of influenzal pneumonitis. The consolidated areas varied considerably in size, frequently involving the greater part of entire lobes. True croupous lobar pneumonia, of the type commonly met with, was relatively rare, occurring only in thirteen instances. In seven of these it formed the only type of pulmonary consolidation, in the six others it was associated with bronchopneumonia.

The incidence of lobar pneumonia in association with influenza epidemics appears to have varied a great deal in different places and times, due probably to coexistence of two separate and distinct infections. Thus, during the Vienna epidemic of 1890, Kundrat<sup>30</sup> found it in one-half of his cases, and others have reported even higher figures. The probable explanation of this high frequency is that during the influenza period there coexisted an epidemic of lobar pneumonia. Opie<sup>5</sup> and his co-workers found thirty-six cases of lobar pneumonia in seventy-nine necropsies. Hall, Stone and Simpson,<sup>29</sup> in thirteen necropsies, found typical lobar pneumonia in eleven cases, and confirmed the diagnosis microscopically. Blanton and Irons,<sup>10</sup> in 123 necropsies, saw it only once. Nuzum,<sup>21</sup> Symmers<sup>11</sup> and others encountered only lobular pneumonia. The condition may be dismissed here with the statement that it presented no unusual feature, and we shall confine ourselves to a description of the influenzal pneumonitis.

The cut surface of the lung was generally very moist and excessively bloody, especially in the cases dying after a relatively short duration of disease. From the inflated anterior edges large amounts of lightly and heavily blood tinged, frothy serum could be expressed. In the posterior two-thirds larger and smaller areas of consolidation were present. These varied in color, size and consistency, resulting in a number of distinct pictures, often within the same lobe. Generally, the consolidated areas were indistinctly outlined and gradually faded into the surrounding hyperemic lung tissue. A marked tendency to become confluent was noted, and pseudolobar involvement occurred very commonly.

The texture was as diverse as the other features; smooth and velvety consolidations bordering on coarsely and finely granular neighboring areas. These granular consolidations resembled in every way the cut surface of a croupous pneumonia, except for their lobular character. The consistency ranged from definite necrotic softening to total firmness, and the color varied through all shades of red and gray. Only exceptionally were the consolidated areas definitely peribronchial. Now and then the interlobar septa were thickened and indurated areas were present. Atelectasis, due to obstruction of bronchial branches, was common, sometimes involving considerable areas. In a general way, the consolidations, according to their extent, might be classified as patchy and confluent or pseudolobar. Table 6 shows that there was but slight difference in the distribution of these two types in the various lobes of the lung; that the upper lobes were somewhat less confluent than the lower lobes, and that the middle lobes were the least affected.

Microscopically, as wide a variation was seen as in the gross appearance. The exudates had, however, sufficiently distinctive character to allow the division into three main groups. In the first, the exudate was chiefly catarrhal, consisting of large, desquamated, epithelial cells. In the second group the same features obtained, with the addition of a heavy fibrin network. In the third group, the exudate was mainly purulent, with the addition of fibrin. All three types often existed in the same lung. Commonly, even the same microscopic section presented all three of them, so that we might, as one of the main characteristic features of influenzal pneumonitis, take the great variation of the exudate. (Figures 13, 14 and 15 were purposely made from the same microscopic section. The various processes were distinct, but almost adjacent to one another.) This is readily explained if we remember that one or more organisms invade these tissues, and that each class of bacteria may set up distinctive inflammatory processes in adjoining or closely placed together alveoli. In addition to the cellular character of the exudates, there was usually a heavy admixture of red blood cells with large amounts of precipitated serum. It is very difficult to estimate the incidence of the three groups of exudates, since they so commonly occur together. By taking several sections from each lung and noting the predominant character of the exudate, the following grouping might be made:

Catarrhal bronchopneumonia.....	34 per cent.
Fibrinocatarrhal bronchopneumonia .....	39 per cent.
Fibrinopurulent bronchopneumonia.....	27 per cent.

Such grouping, however, is only highly approximate and represents but the predominating character of the exudate in the majority of the sections examined. Fibrin, in varying amounts, could practically always be found in some sections, and in over two-thirds of the cases it was prominent. The exudates of the more catarrhal types generally presented pronounced swelling of the lining epithelium (Fig. 12), and not infrequently groups of alveoli were lined with huge cuboidal cells, giving the appearance of tubules and resembling the condition of the fetal lung. Such changes, as is well known, are often seen after indu-

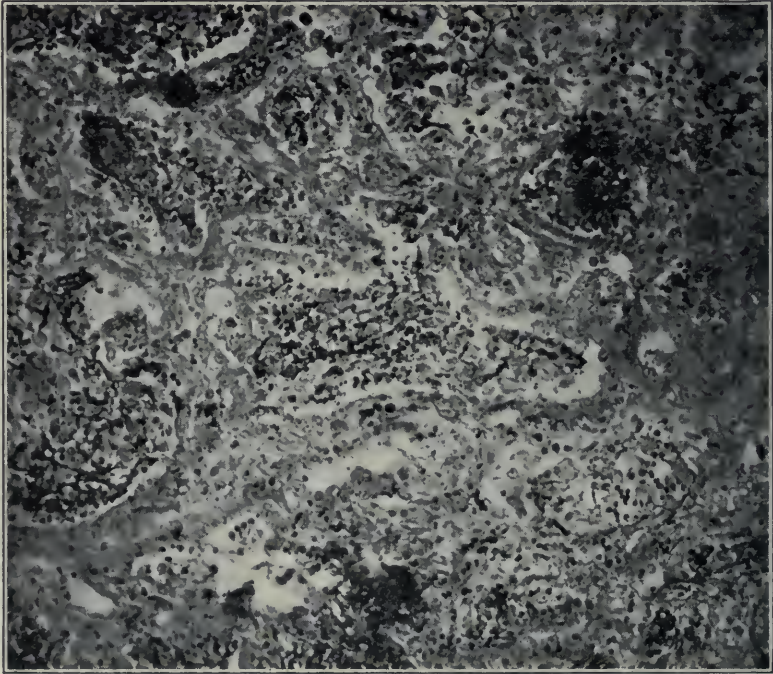


Fig. 12.—(Lung.) Hyperplasia (anaplasia?) of pulmonary epithelium. Note the uniform hyperplasia of the epithelial lining. This photograph does not represent the most pronounced proliferation, but the average.

rative bronchopneumonic processes, but only rarely is this extreme proliferation encountered in an acute pneumonitis. In some sections the condition was so uniform as to make one consider the possibility of a reversion to fetal types, an anaplasia produced by excessive stimulation of the lung epithelium. It is doubtful whether such anaplastic changes ever occur in acute inflammations, and our statement here is merely an analogy.

In sections where definite fibrosis was present—usually in cases where the pulmonary infection had persisted for a relatively consid-

erable time—such proliferation of the lining membrane was likewise frequently encountered. Occasionally the alveolar membrane was intact, but more generally a part, at least, was desquamated, and these huge cells were lying free in the air sacs (Fig. 13).

All stages of cellular degeneration could be observed, the most noteworthy being vacuolization with shrinkage of the nucleus. Phagocytosis was often seen; the phagocytized structures being most often red blood cells, polymorphonuclear leukocytes and cellular debris. Bacterial phagocytosis was relatively infrequent in the large cells, but

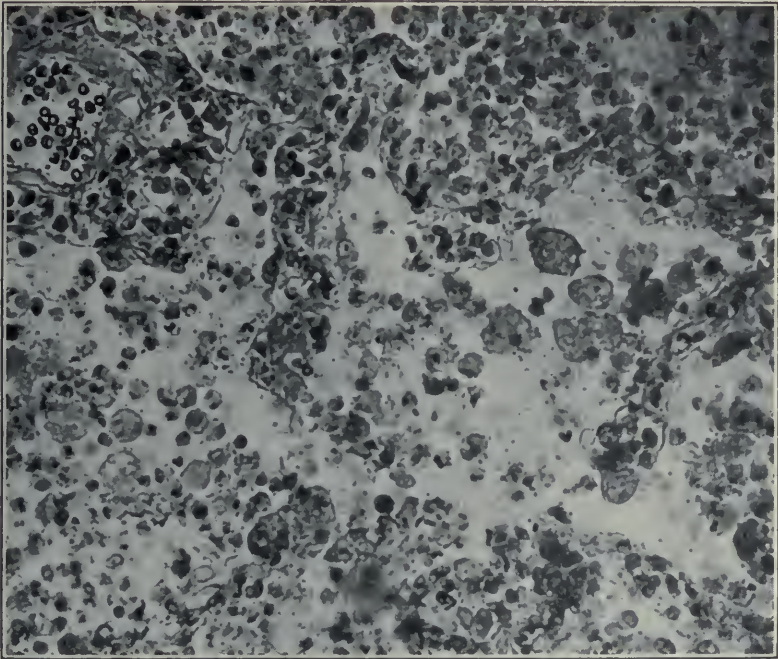


Fig. 13.—(Lung.) Catarrhal bronchopneumonia. Note presence of huge, often vacuolated, desquamated epithelial cells. Fibrin is absent. The alveolar capillaries are markedly distended.

quite common in polymorphonuclear leukocytes. Sometimes the epithelial cells were fused together, forming huge, syncytial masses, apparently consisting of from three to five fused cells and measuring up to 60 microns in diameter. These giant structures frequently contained inclusions of red cells and leukocytes, and are probably degenerative in character. Besides the lining cells the exudate consisted chiefly of precipitated serum and red corpuscles, polymorphonuclear elements being uncommon. Definite hemorrhages were frequent and often involved large areas. The alveolar capillaries were hugely dis-

tended and often contained hyaline conglutination thrombi. Generally, the walls were well preserved and cellular infiltration was rare. The perivascular and peribronchial spaces contained cells of the same type as those described.

This catarrhal type of pneumonitis predominated early in the epidemic and throughout the epidemic in patients dying after a relatively short illness, and we believe that the changes enumerated are more directly due to the virus of influenza than to the associated bacteria. In fact, we are convinced that the pronounced epithelial proliferation and the marked hyperemia constitute the essential early lesions of true influenza.



Fig. 14. — (Lung.) Fibrinocellular bronchopneumonia. Note network of fibrin and presence of large epithelial cells. This was the most common picture seen in influenzal bronchopneumonia.

The second type of pneumonitis was fibrinocatarrhal in character, and differed from the preceding not only in the addition of large amounts of fibrin, but in cellular reaction. Catarrhal cells were still present in relatively large numbers and presented the general characters mentioned above, excepting that more intense degenerative changes were seen. The fibrin occurred in the form of dense networks, consisting sometimes of fine, sometimes coarse, strands (Fig. 14), and it was generally more pronounced at the periphery of the air cells.

Polymorphonuclear cells were present in greater numbers than in the preceding forms. Red blood cells were abundant, but generally not so excessive as in the preceding type. The alveolar walls were frequently ruptured and infiltrated with mononuclear and polymorphonuclear leukocytes, and often showed a fibrin network. We look on this type as an intermediate stage in the disease process.

The third group was fibrinopurulent or purulent in character, the exudate containing relatively few epithelial cells, while polymorphonuclear leukocytes were abundant (Fig. 15). Fibrin was present in varying amounts. The alveolar contents were rarely hemorrhagic,

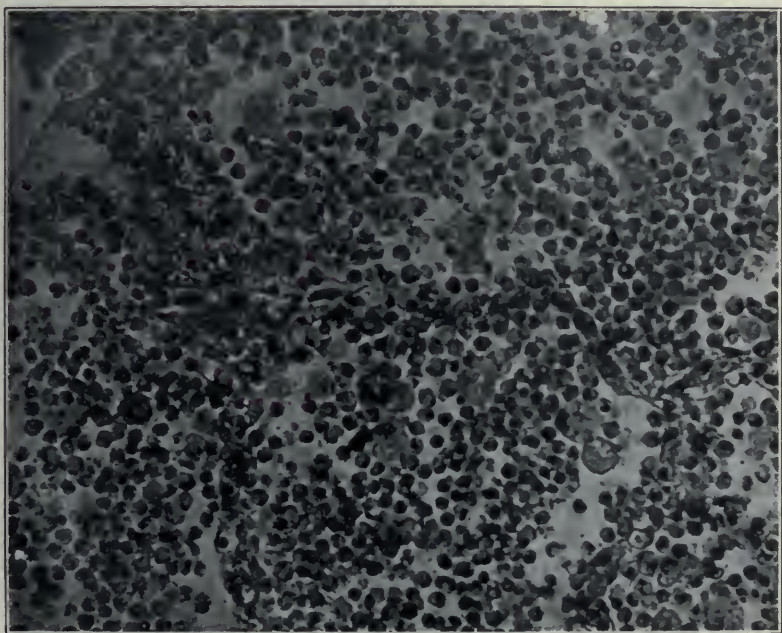


Fig. 15.—(Lung.) Suppurative bronchopneumonia. The cellular exudate consists chiefly of polymorphonuclear cells, with here and there a few large degenerated epithelial cells.

though sometimes a few red cells were seen. Serum was seldom as pronounced as in the earlier stages. Typical plasma cells were frequently observed in considerable numbers in the exudate as well as in the lymphatics and alveolar walls. These last often showed widespread destruction, and large areas of necrosis were often seen (Figs. 16 and 17).

Fibrosis was not infrequent. The bronchial walls were often entirely destroyed and abscesses were many times encountered. We consider this the end stage of influenzal pneumonitis. It occurred at

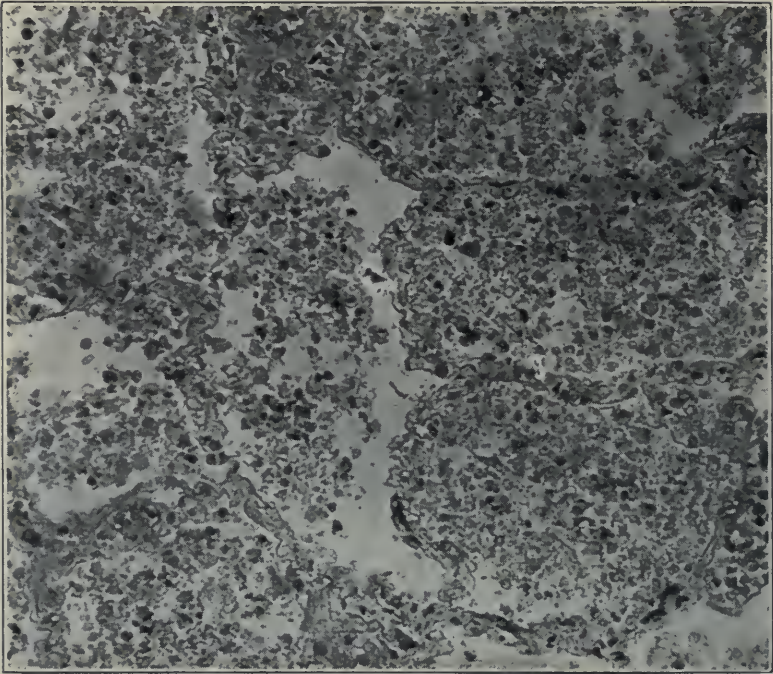


Fig. 16.—(Lung.) Suppurative pneumonia with partial destruction of the alveolar wall. The exudate here is older than in the preceding figure, and the various cells are considerably more degenerated.

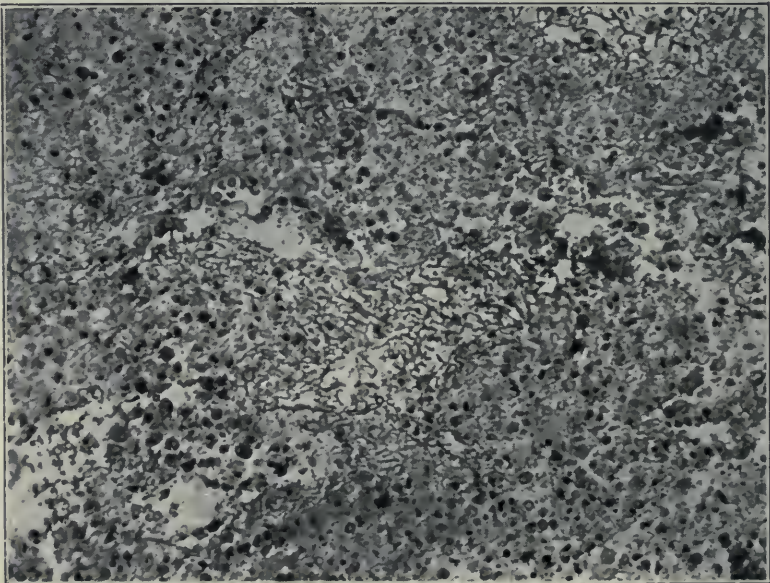


Fig. 17.—(Lung.) Suppurative bronchopneumonia with areas of necrosis. The alveolar walls here are entirely destroyed and necrotic areas are everywhere seen. This is a later stage than that shown in the preceding figure.

a later period in the epidemic when the duration of the illness was considerably longer than in the earlier part of the epidemic, and when the pneumonic processes had persisted for some time. It is the second and third type of influenzal pneumonitis which is probably produced by the commensals of the virus of influenza.

TYPES OF INFLUENZAL PNEUMONIA ACCORDING TO THE  
ORGANISMS PRESENT

An attempt was made to correlate the anatomic findings with the bacteriologic results, and to classify the types of pneumonitis encountered according to the bacteria present. As will be seen in the bacteriologic part of this paper, the micro-organisms which were most often isolated were: *B. influenzae*, hemolytic and nonhemolytic streptococci, pneumococcus of various types, *M. catarrhalis* and staphylococcus. These were usually present in various combinations. Indeed, it was not uncommon to find most or all of them in cultures from the different lobes of the same lung. It was, therefore, exceedingly difficult to attribute this or that anatomic change to any special bacterial type. The fact that all of these bacteria must be looked on as commensals, or as secondary or tertiary invaders of the pathologic tissue prepared by the virus of influenza, make separation on an etiologic basis generally quite impossible. MacCallum,<sup>44</sup> who classified his cases, apparently had less of a mixture of bacteria than were present in our series, and he was able to separate the types of pneumonitis caused by the pneumococcus, streptococcus and the influenza bacillus.

It was the custom here to take cultures from all lobes of the lungs, as well as from the principal organs. In only two instances were pure cultures of the influenza bacillus isolated; once the staphylococcus, once *M. catarrhalis*, five times the nonhemolytic streptococcus and somewhat more frequently the pneumococcus and hemolytic streptococcus were found in an unmixed form in the lungs and elsewhere. If we add to this the difficulty in isolating this or that bacterium we introduce an added source of error; nevertheless in the patients where pure cultures of one type were obtained, a correlative study was undertaken.

We have already stated that it was not uncommon to find several distinct types of exudates within the same lung, and even within the same microscopic section, and it was not surprising, therefore, to obtain the same results when comparison of the anatomic and bacteriologic studies was undertaken. Thus, for instance, in the two cases where *B. influenzae* occurred in pure culture, the exudate was fibrino-catarrhal in the majority of sections of one case, and purulent, with relatively small amount of fibrin, in the other. The same condition

was present in the staphylococcus and *M. catarrhalis* cases, while in the pneumococcus and hemolytic and nonhemolytic streptococcus cases, the results were even more confusing. Thus, in nineteen cases where the hemolytic streptococcus predominated, the lung exudate in the majority of the sections was catarrhal eight times, fibrinocatarrhal five times, fibrinopurulent four times, purulent with areas of necrosis twice. The nonhemolytic streptococcus and the pneumococcus cases showed a similar discrepancy. It seems, therefore, it is not feasible to divide the pneumonitis of influenza on bacteriologic basis excepting in a general way, and this we can do by considering the mixtures of bacteria that predominated at the various stages of the epidemic and in the different periods of the disease, remembering always that we deal with a definite morbid process, more or less modified by commensal or invading organisms.

In this general way we feel that the first picture of influenzal pneumonitis, chiefly catarrhal in type, was produced mainly by the *B. influenzae* and the nonhemolytic streptococcus (Figs. 12 and 13). The second form of pneumonitis, fibrinocatarrhal, was probably the result of pneumococcic and nonhemolytic streptococcic activity (Fig. 14), while the last form, fibrinopurulent or purulent in character (Figs. 15, 16 and 17) had the staphylococcus, *M. catarrhalis* and hemolytic streptococcus as the chief invasive factors. Further than this we do not feel justified in going, and it seems to us that in the multiformity of lung changes present lies the chief characteristic of influenzal pneumonitis. In other places, where fewer micro-organisms are endemically or epidemically present, a separation into distinct types is, of course, possible, and should rightly be undertaken. The diversity of the pathologic and bacteriologic picture in this and preceding epidemics speaks for the pleomorphic character of the disease.

*Spleen.*—The statements in the literature concerning the size of the spleen vary greatly, and this Kuskow,<sup>2</sup> who seems to have studied the subject most thoroughly, explains as depending on the severity of the epidemic or on individual cases. According to him, during the epidemic of 1889-1890 in France the spleen was increased to twice its size and more. In Switzerland, Finland and Russia the majority of the authors found the spleen rarely enlarged, and sometimes decreased. In his own forty cases (Russia) the spleen was actually smaller, and very markedly decreased in size in twenty-eight. In the present American pandemic slight enlargement seems to have been the rule, with relatively few acute splenic tumors (Blanton and Irons,<sup>10</sup> Symmers<sup>11</sup>). The details of our findings were calculated for sixty-eight cases (Table 7). In ten of these cases the spleen weighed less than 150 grams, in thirty-one it weighed between 150 and 249 grams, with

an average of 195 grams. In twenty-five it weighed between 250 grams and 449 grams, with an average of 321 grams. In two cases it weighed more than 450 grams, with an average of 590 grams. Further data as to weight and measurements are given in the table. It would seem then, that in more than 80 per cent. of the cases the spleens were definitely enlarged, and in almost one-third of the total number they were considerably increased in size. Definite diminution never occurred, the spleen in no instance weighing less than 100 grams.

The capsule was generally tense, the external color reddish brown to purplish red, consistency slightly flaccid, occasionally much softened. The cut surface was usually uneven, moist and often very bloody. The

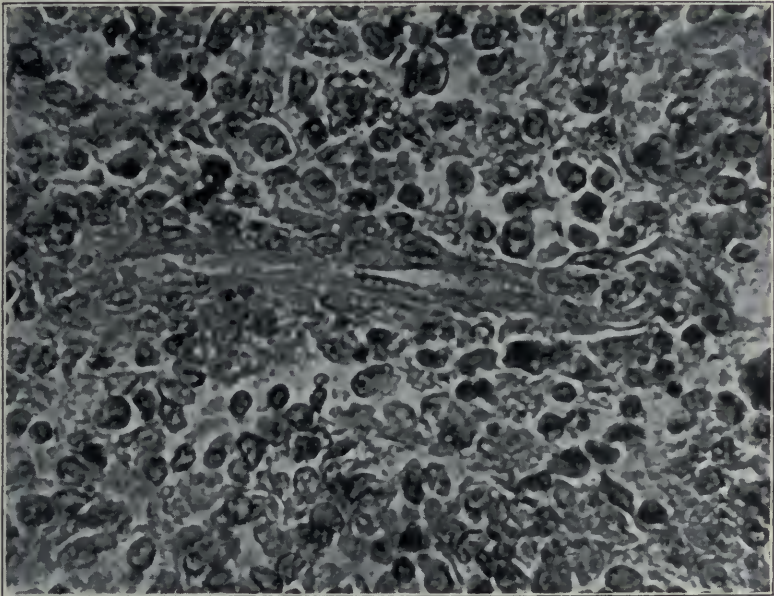


Fig. 18.—(Spleen.) Note swelling of arterial lining. The vascular lumen is almost occluded.

trabeculae could only rarely be recognized distinctly. The follicles were plainly visible or somewhat prominent in fifty-seven instances, and indistinct or entirely obscured in sixty-nine instances. The pulp was usually softened, and in about 20 per cent. of the cases it was definitely mushy. The duration of the disease process, the period of the epidemic, the size of the spleen and its follicular or diffuse character did not appear to exhibit any constant relation. Microscopically, the commonest change consisted in the excessive blood contents; often large areas were flooded with red cells, constituting undoubted hemorrhages, many of these cells being shadow rings. An endothelial hyper-

plasia of the vessels and sinuses was usually present and often pronounced (Fig. 18). Oftentimes desquamated endothelial cells were found free in the venules and arterioles, occasionally obstructing their lumen; hyalin and conglutination thrombi were likewise present. Widespread necrosis of the reticulum commonly occurred, partly due, probably, to the hemorrhages and partly to toxic action. Now and then the arterial walls presented a smooth, homogeneous staining, evidencing toxic hyaline degeneration. Elsewhere definite hyperplasia was present, manifesting itself by greatly increased numbers of large mononuclear splenic cells. Polymorphonuclear cells were rarely met with, and then only in small numbers. The malpighian bodies were

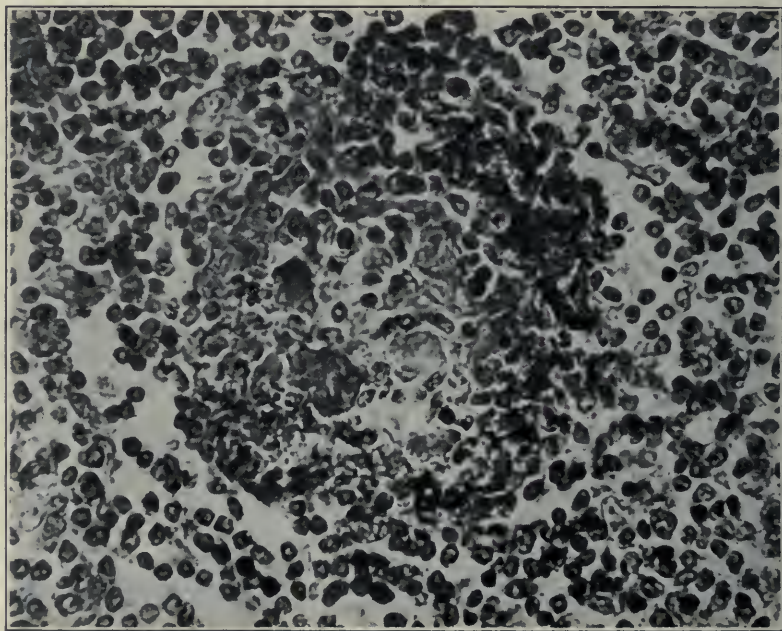


Fig. 19.—(Spleen.) Beginning hyalin degeneration of germinal centers of follicles. Note the huge, even-staining cells in center of photograph. This is the early stage of the process shown in Figure 20.

generally loosely arranged, with many large, pale staining, germinal lymphocytes. Within the follicles one frequently encountered eosin staining, smooth, hyaline areas, occasionally of considerable size. On minute inspection these areas seem to be composed of huge partly fused, indefinite staining, degenerating cells (Figs. 19 and 20). Similar necrotic areas have been found in diphtheria, scarlet fever and other acute infections (McCallum<sup>45</sup>).

45. McCallum, W. G.: Textbook of Pathology, Philadelphia, W. B. Saunders Co., 1916.

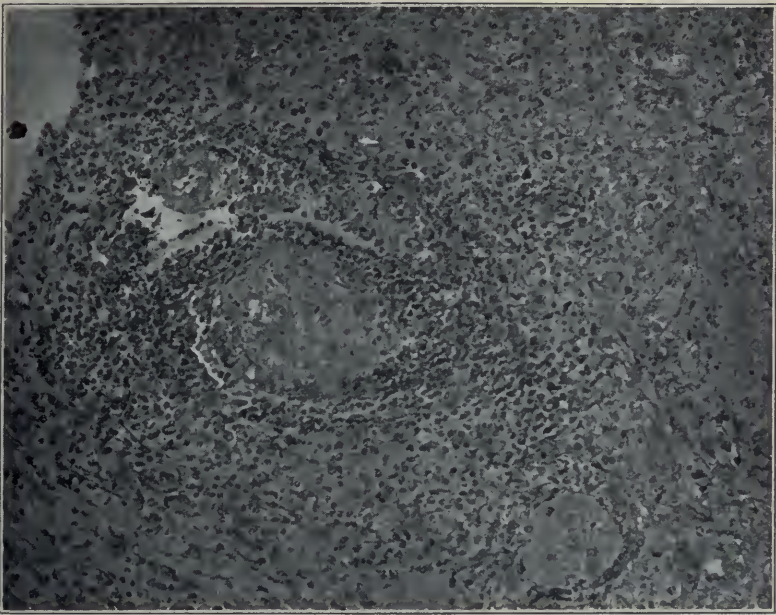


Fig. 20.—(Spleen.) Toxic hyaline degeneration of germinal centers of splenic follicles. This represents a later stage of the preceding figure. Note that the entire germinal center consists of fused degenerated cells; a few of the nuclei are still present.

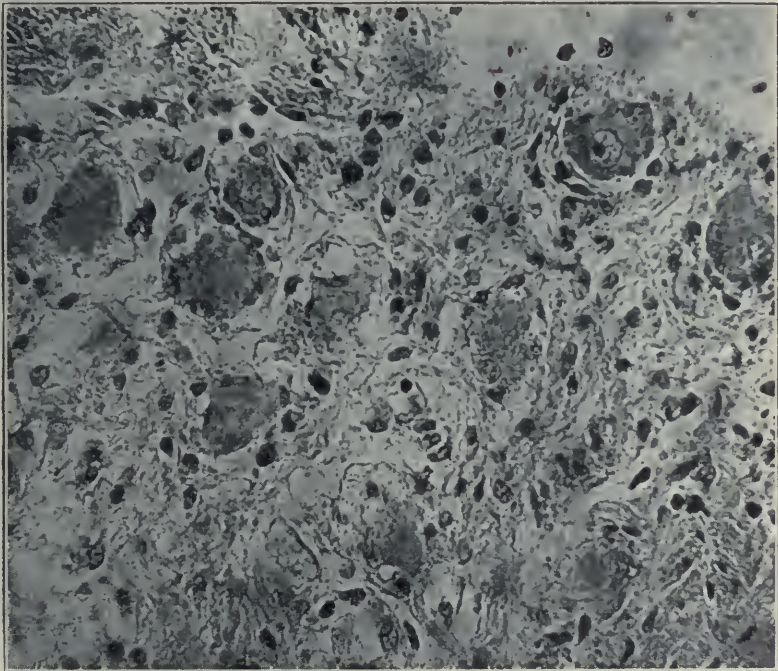


Fig. 21.—(Semilunar ganglion.) Acute cloudy swelling and degeneration of ganglionic cells. All stages, from simple cloudy swelling to almost total disappearance of the cells, are shown. Note the nuclear changes varying from eccentric position (middle of photograph) to total chromatolysis (left side of photograph). Compare the cellular changes with a nearly normal cell shown in the upper right corner of the photograph.

*Semilunar Ganglia.*—These structures in practically every instance were slightly swollen and occasionally of a faint pink color. There was no appreciable change in the consistency. The cut surface was usually moist, often decidedly pinkish, and a number of bleeding points were always seen. Microscopically (Fig. 21), the ganglion cells were swollen, devoid of definite outline, with a granular cytoplasm which stained poorly and did not show Nissl granules. The nuclear changes varied from loss of nuclear outline to poor or excessive staining, granularity, and often total disappearance of the nucleus. The nucleoli, as a rule, remained, but occasionally they likewise disappeared. Extreme changes consisted in loss of the entire cell. The above enumerated

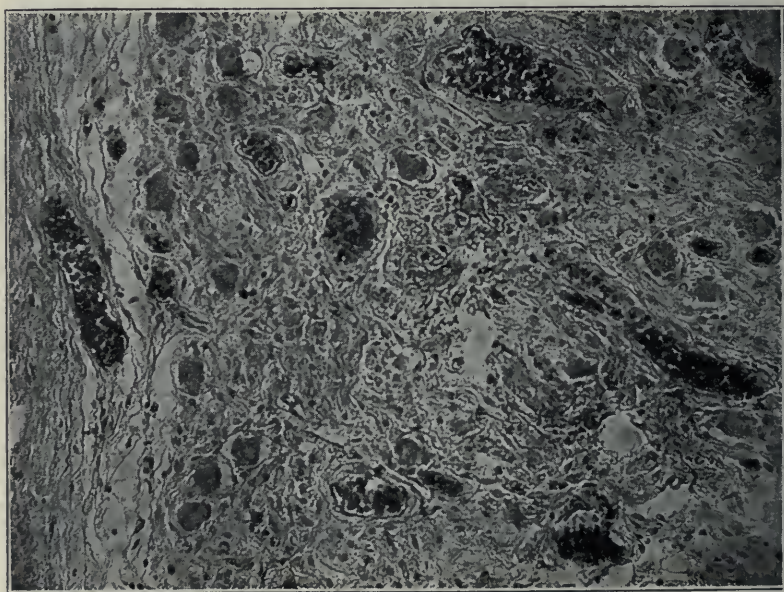


Fig. 22.—(Semilunar ganglion.) Marked congestion and degeneration of ganglion cells. The cellular changes are similar to those pictured in the preceding photograph. Note dense congestion of vessels.

alterations usually affected only isolated cells or groups of cells, for in other parts of the section the structures were normal. The condition was comparable to the ganglionic changes in the cerebral cortex and seems to point to the widespread toxic effects of the virus. The vascular changes were similar to those described in other organs, such as definite hemorrhages and practically always, marked congestions (Fig. 22). Occasionally, the perivascular lymphatics were dilated and packed with large and small round cells. The interstitial substance was often loosely arranged.

*Suprarenals.*—In three instances frank hemorrhages in the suprarenal substance, enlarging the organ to about twice its normal size, were present. In twenty cases the suprarenals showed no gross changes. In the remaining 103 cases there was slight increase in size and definite congestion. In these latter cases the outside color was pinkish brown, and the cut surface decidedly bloody. The outer zone of the cortex was generally narrow and pale grayish yellow, rarely presenting the deep orange yellow tint so frequently seen in the suprarenal cortex. The intermediate zone was a deep reddish brown and exuded blood, while the medulla varied from a reddish gray to a deep red. Microscopically, extreme congestion and frequent small hemor-

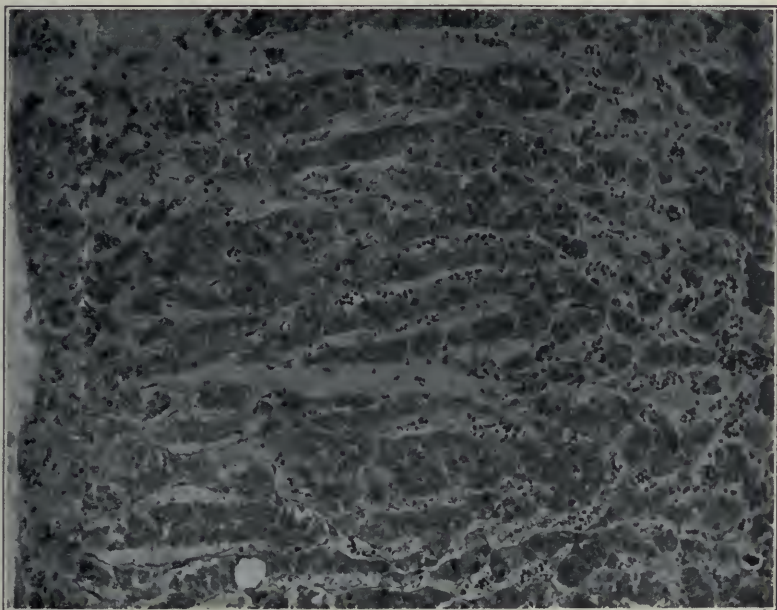


Fig. 23.—(Suprarenal.) Lipoid exhaustion. Note absence of lipoid granules, moderate edema, and, in places, cellular swelling and loss of outline.

rhages were found, usually involving the medulla and intermediate zone. The cells of the cortex appeared slightly swollen and usually devoid of their lipoid granules. This lipoid exhaustion was observed almost constantly (Fig. 23). Other cells appeared in the state of acute cloudy swelling, with indefinite cell outlines and poorly staining nucleus. The interstitial substance was usually arranged loosely and was definitely edematous. Focal necrosis, with small round cell infiltrations, was occasionally observed. In a number of the gland cells, especially of the cortex, numerous deep blue staining, coarse granules were encountered. We shall refer to this in the discussion of the liver, where

similar granules were often observed. Very occasionally diffuse infiltration with polymorphonuclear cells, pointing to an acute inflammatory suprarenalitis, was seen.

*Genito-Urinary Tract.*—*Kidneys:* The details of the weights and measurements were tabulated for fifty pairs of kidneys, and are given in Table 7. In 10 per cent. both kidneys weighed less than 150 gm. each. In eighty-six, or 88 per cent., the weight of each organ averaged 202 and 207 gm., respectively. In four, or 2 per cent., respectively, each organ weighed 210 gm. Both kidneys were of the same weight in 7 per cent., the left was heavier than the right in 54 per cent. and the right kidney heavier than the left in 39 per cent. of the cases.

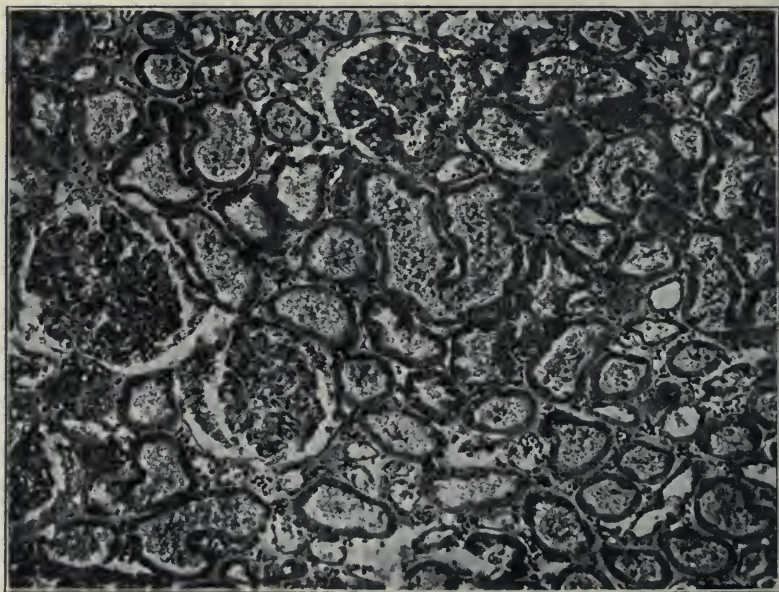


Fig. 24.—(Kidney.) Acute parenchymatous degeneration. Note presence within tubules and capsular spaces of granular precipitate. The epithelial lining is frequently degenerated and often necrotic. The capsular epithelium is somewhat precipitated.

The measurements corresponded to the size and are given in the table. This means that in 90 per cent. of the examinations the kidneys were somewhat increased in size or weight. In every instance parenchymatous changes, usually of mild degree, but often quite severe, were observed. It was not possible, grossly, and frequently impossible minutely, to decide whether the condition present should be looked on as an early parenchymatous nephritis, or as a transitory cloudy swelling. Definite nephritis was present in about 10 per cent. of the cases, but generally the organs were flaccid, with an easily stripping

capsule, leaving a smooth, grayish red, often mottled, surface, on which the stellate veins often stood out prominently. The cut surface was, as a rule, moist and bloody. The cortex was usually moderately increased in width, the cut edges gaping slightly, and, in a number of cases, considerably. The glomerular markings were sometimes washed out, but at other times very definite, and, in a considerable number of instances, the glomeruli and cortical striations were prominent. The corticomedullary junction was, as a rule, very indefinite. The medullary junction was usually very indefinite. The medullary striations varied, but, as a rule, were distinct. The pelvic mucosa usually presented injection, and, in about 30 per cent. of the cases submucous, petechial hemorrhages were encountered.

Microscopically, the kidney picture was quite uniform, varying only in degree (Fig. 24). The interstitial substance was moderately edematous, the glomeruli where large, the capsule of Bowman was not thickened. The capsular epithelium was swollen and proliferated in about 20 per cent. of the cases. Multiple layers of capsular epithelium were met with in a few instances. The capsular space, in 50 per cent. of the cases, contained a granular, eosin staining precipitate. The tufts were large because of vascular congestion. The endothelium was swollen with large nuclei, but there was no evident active multiplication. Frequently, hyaline and conglutination thrombi were seen. The tubular epithelium was generally swollen, the cell outlines poor, the cell borders ragged and the lumen filled with granular debris. Often vacuolization was observed. The nuclear changes ranged from poor staining reactions to total absence. In one instance, a large part of the kidney appeared necrotic. Small microbic abscesses were present in only one instance (Fig. 25). In every case the convoluted tubules were more affected than the straight tubules. The degeneration and necrosis of the epithelium was rarely uniformly distributed, sometimes entire tubules, or groups of tubules, were attacked, with apparently normal epithelium in close proximity. It would seem from the literature that acute nephritis appears less frequently than in most infectious diseases. During the epidemic of 1889 and the succeeding years the changes found closely resembled those seen here. Thus, Wallis,<sup>24</sup> Ribbert,<sup>22</sup> Weichselbaum,<sup>25</sup> Kuskow,<sup>2</sup> and others reported cloudy swelling, with occasional glomerular nephritis. Hemorrhagic nephritis appeared uncommon.

Total necrosis of an entire kidney was described by Beneke<sup>46</sup> and once by Kuskow.<sup>2</sup> The former compared this to the necrosis resulting from ligation of the renal vessels and believed it to be due to vascular spasms. No explanation can be offered as to the necrosis in our case,

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46. Beneke: Schmidt's Jahrb. **226**: p. 111.

but it was probably toxic rather than infectious. Stone and Swift,<sup>13</sup> in fifty-five necropsies, found acute parenchymatous nephritis twenty-three times and cloudy swelling twenty times (gross diagnosis). Dever, Boles and Case,<sup>47</sup> in two necropsies, found well marked parenchymatous nephritis. Nuzum<sup>21</sup> and his co-workers report the kidneys heavier than normal and the seat of a parenchymatous degeneration. Blanton and Irons,<sup>10</sup> in 123 necropsies, found acute nephritis in three and cloudy swelling of the kidneys in twenty-one cases. Symmers,<sup>11</sup> in twenty necropsies, observed changes comparable to those seen here. The kidney changes observed here and elsewhere during the epidemic seem to be of the nature of a parenchymatous degeneration, with edema, rather than of a productive nephritis, although this too has occurred several times.

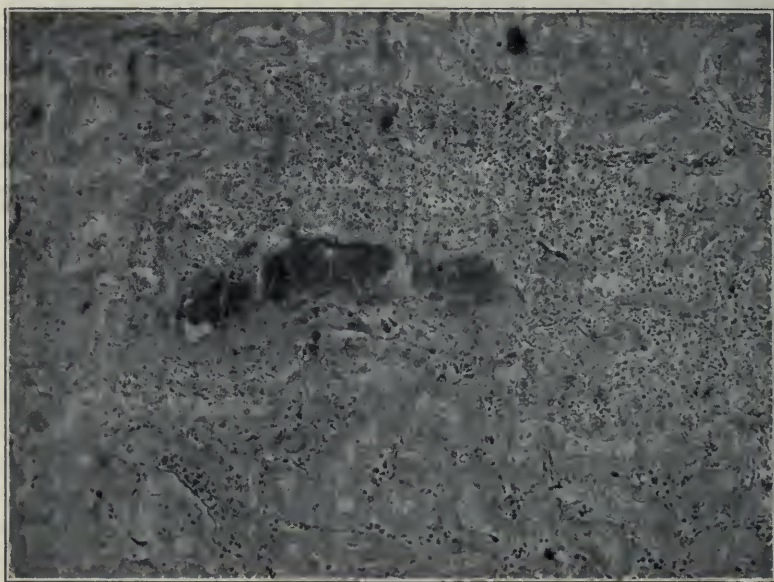


Fig. 25.—(Kidney.) Bacterial embolism and abscess. Note darkly stained bacterial mass and surrounding necrosis and cellular infiltration.

*Ureter, Bladder and Prostate.*—The ureter, in its upper fourth, frequently showed submucous, hemorrhagic extravasations, similar to those observed in the renal pelvis. The rest of the mucosa was occasionally moderately injected. The urinary bladder was similarly affected, showing injection, and commonly submucous, petechial hemorrhages.

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47. Dever, Francis J., Boles, Russell S., and Case, Eugene A.: Influenza at the U. S. Naval Hospital, League Island, Va., J. A. M. A. **72**:265 (Jan. 25) 1919.

*Prostate.*—No gross nor microscopic changes were observed, with the exception of slight congestion. The prostatic acini presented no noteworthy alterations.

*Seminal Vesicles, Spermatic Cords and Testicles.*—The seminal vesicles were generally filled with a viscid, sometimes slightly turbid fluid. The spermatic cords presented no gross changes. The testicles very frequently possessed a moist, definitely bloody, cut surface and were of softened consistency. The cells, microscopically, were commonly swollen and ragged; cessation of spermatogenesis was frequently seen.

*Gastro-Intestinal Tract.*—Tongue: The tongue was often reddened, but no characteristic changes, as in typhoid or scarlet, were observed. The mucosa of the mouth and posterior pharynx was likewise often reddened. Microscopically, the lymphoid tissue was frequently very prominent. This same condition has been observed by Oberndorfer,<sup>27</sup> but the youthful age of our patients makes it unlikely that we are dealing with a pathologic change, although the lymph tissue generally in the body is proliferated above the normal state for the age of these patients.

*Tonsils and Thyroid.*—An acute tonsillitis was occasionally encountered, but it is probably coincidental. The thyroid was now and then somewhat enlarged, but presented no noteworthy microscopic changes.

*Pharynx, Esophagus and Stomach.*—The mucosa was frequently dusky. The lymph follicles, in the lower part of the esophagus, were usually prominent. In the stomach we found almost constantly extensive submucous, petechial, hemorrhagic extravasations, not confined to the dependent parts, and probably not postmortem in origin since they were found in bodies necropsied within an hour or so after death. The condition is comparable to the hemorrhagic extravasation noted beneath mucous and serous surfaces and in the skin. The stomach contents, which were generally fluid, often had a light brown or reddish brown tint, due, probably, to slight leaking of the extravasated areas. No other gross or microscopic changes occurred.

*Liver.*—The details of the weight and size of the liver were estimated in sixty-one instances. In 7 per cent. the liver weighed less than 1,500 gm.; in 47 per cent. the weight averaged 1,829 gm.; in 46 per cent. the weight averaged 2,254 gm. Further details are shown in Table 7. In over 90 per cent. of the cases the liver was definitely increased in size and weight. Nuzum,<sup>21</sup> Lyon<sup>6</sup> and others found the liver likewise heavier than normal. The consistency was generally flaccid, occasionally definitely soft. The lower edge was, as a rule, rounded, the capsule smooth and translucent and the subcapsular lobu-

lation generally indefinite but sometimes prominent. The cut surface was generally slightly but frequently considerably bloody. The lobulation appeared washed out. The translucency of the tissue was, in the majority of instances, dull, gray and often parboiled. In about one-third of the cases the centers of the lobules were large and deeply congested. Frequently, especially near the periphery of the organ, pale, yellowish fatty areas were seen. In a number of cases lobulation appeared usually distinct, the centers being very large and dull brownish red or yellowish red, with a narrow, grayish brown peripheral zone. Very exceptionally the surface possessed a fatty sheen; evidences of biliary pigmentation were never observed grossly.

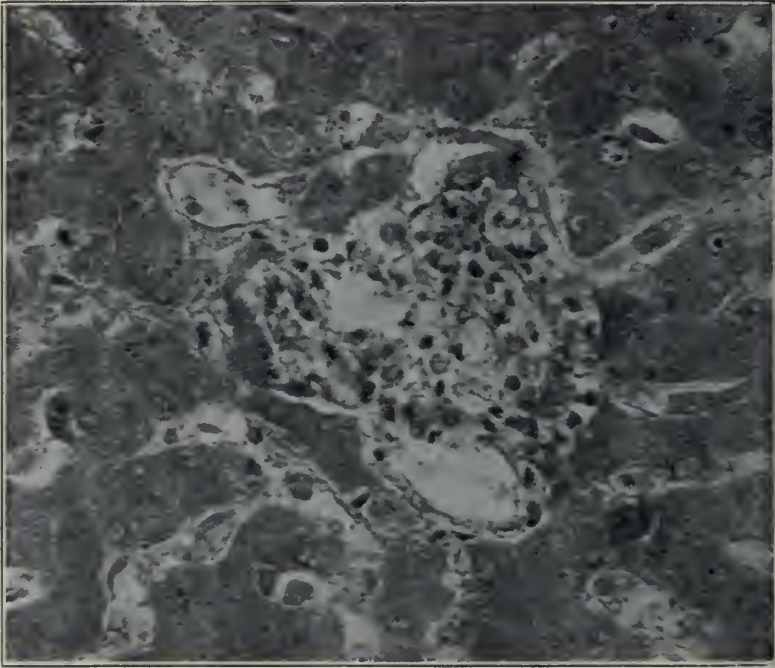


Fig. 26.—(Liver.) Small focal necrosis. The necrotic areas here involve only a small part of the liver lobule. A few round cells and some degenerating nuclei are present in the necrotic area.

Microscopically, the principal change was albuminous degeneration, the cells being large, with cloudy cytoplasm, the nucleus presenting various degenerative changes. Inconspicuous biliary pigmentation was common but not prominent. A few areas of fatty infiltration were frequently seen, but this was never excessive. Fatty degeneration was rare, but hydropic degeneration was common. In fully 50 per cent. of the cases areas of focal necrosis were present. In 11 per cent. these

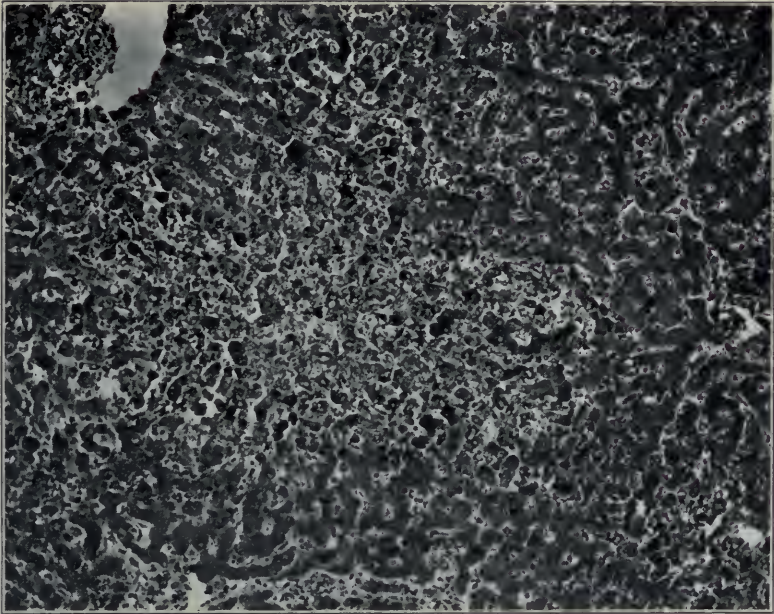


Fig. 27.—(Liver.) Acute toxic central necrosis. The necrotic area involves about two thirds of the liver lobule. The cells in this region show various stages of degeneration, ranging from multiple vacuolization (fatty degeneration) to entire disappearance of the cell. This condition may be looked upon as the preceding stage of acute yellow atrophy illustrated in Figure 28.

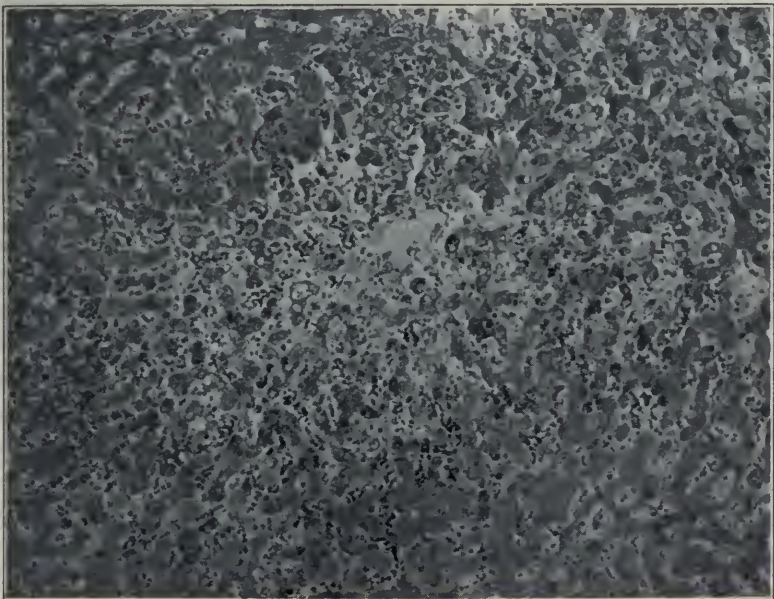


Fig. 28.—(Liver.) Acute toxic central necrosis. This illustrates a somewhat more advanced condition than shown in Figure 27.

were pronounced and large, and, in one instance, a marked acute, yellow atrophy was present. The focal necroses, in the majority of instances, were relatively small (Fig. 26), involving only groups of a few liver cells, but all degrees were present (Figs. 27 and 28) with an extreme condition in one case where practically no normal liver cells occurred (Fig. 29). The necrotic tissue consisted of structureless, eosin staining cells, intermingled with free nuclei, lymphocytic elements and moderate numbers of plasma cells with relatively few polynuclear elements. In the cases of acute yellow atrophy all but the periphery of the lobules was destroyed, the peripheral cells being swollen and

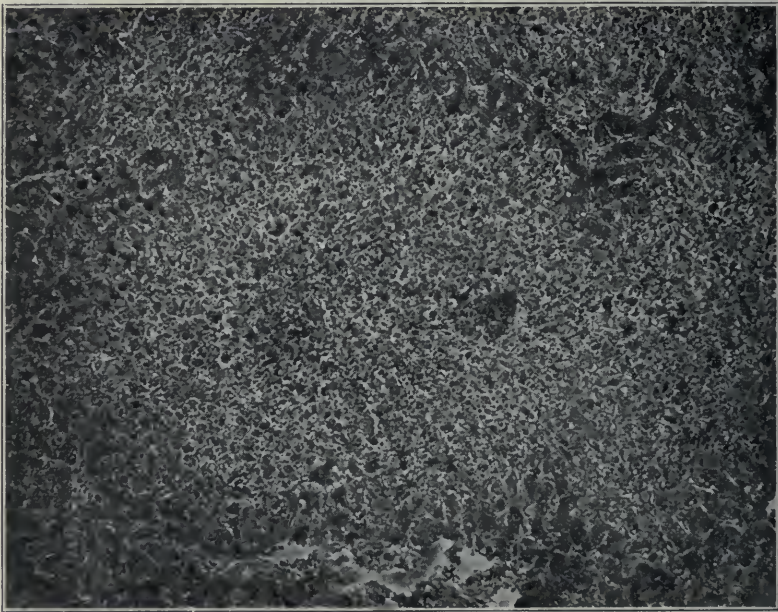


Fig. 29.—(Liver.) Acute yellow atrophy. Practically no normal liver tissue is present. Here and there multi-vacuolated and partly degenerated liver cells are shown near the periphery of the lobules. For the details see Figure 30.

multivacuolated and presenting pronounced nuclear changes (Fig. 30). The Kupfer cells throughout the liver, but especially in the necrotic areas, possessed swollen, oval nuclei and large amounts of cytoplasm. Red cells were present in moderate numbers. The gross appearance of this liver gave little evidence of the excessive microscopic changes. It weighed 1,925 gm., was softened, of reddish brown color, the cut surface presenting very large, reddish brown lobular centers with a pale periphery. Kuskow<sup>2</sup> usually found albuminous degeneration, often focal necrosis, but never fatty degeneration.

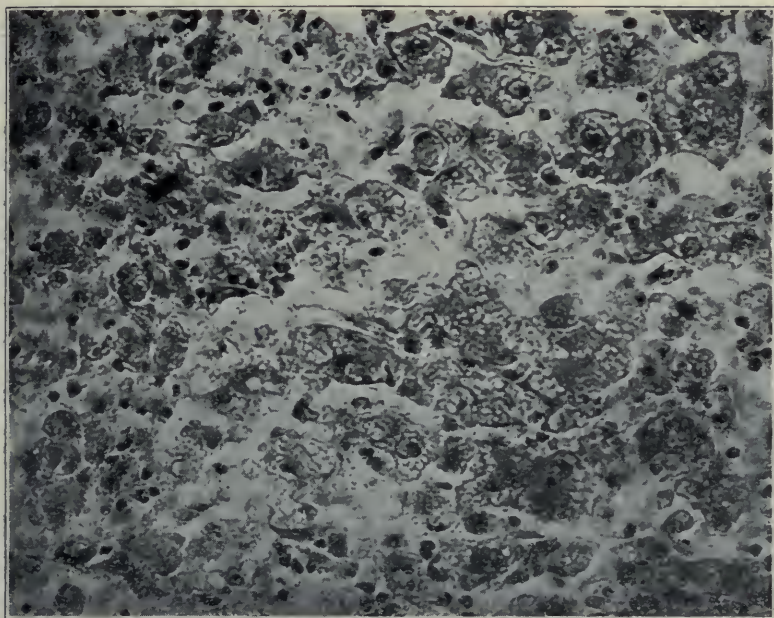


Fig. 30.—(Liver.) Acute yellow atrophy. This photograph illustrates the condition of the cells at the periphery of the necrotic areas shown in Figure 29. Note the marked fatty degeneration and nuclear changes.

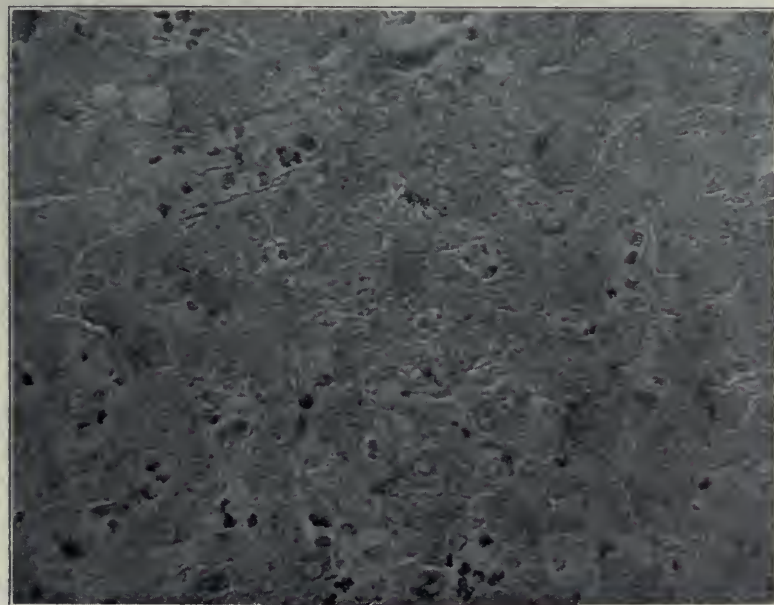


Fig. 31.—(Liver.) Bacterial phagocytosis and lysis by liver cells. Note dark granules in cytoplasm. These granules stain blue with basic dyes.

Frequently, the liver cells contained fine, blue-staining granules (Fig. 31). Searching with the oil immersion lens one occasionally saw small groups of micrococci in the sinusoids, and it seems that these granules were similar to those described by Adami<sup>48</sup> in his subinfection theory as being the final stages of bacterial destruction. The same doubtless holds true of the blue granules described in the adrenal. Sometimes this condition could be studied exceptionally well, especially when only small numbers of micro-organisms were present in the sinusoids, for here all stages of bacterial lysis could be observed in the adjoining liver cells. The periportal connective tissue was rarely

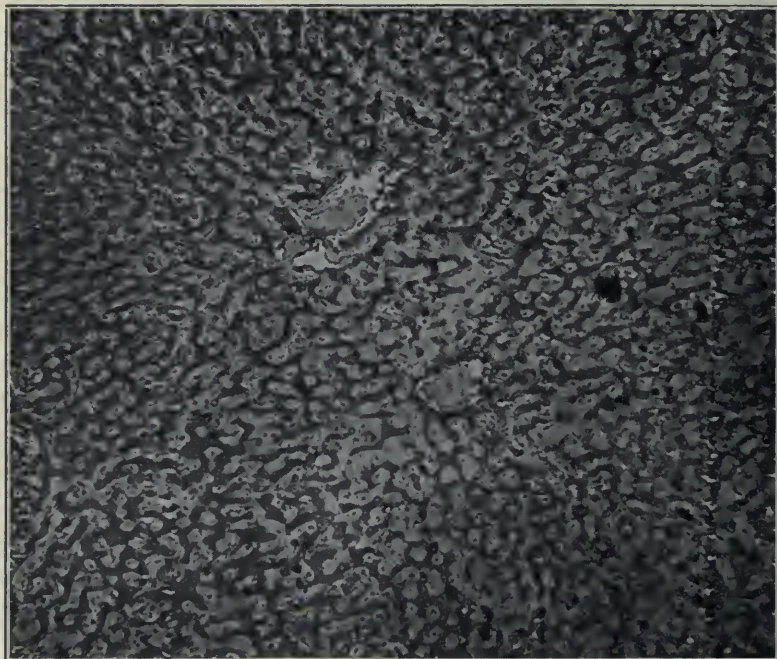


Fig. 32.—(Liver.) Intense congestion, conglutination and hyaline thrombosis. Note that the red cells in the sinusoids and venules have fused into a smooth hyaline mass.

proliferated, but occasionally a lymphocytic or leukocytic infiltration of unimportant degree was observed. The number of biliary ducts was never increased, but in extensive necrosis there was a swelling, without multiplication of the component cells. The vascular changes were similar to those described elsewhere, and frequently consisted of intense congestion and hyaline or conglutination thrombosis (Fig. 32).

48. Adami, J. George: Principles of Pathology, Philadelphia, Lea and Febiger 1:425, 1909.

*Pancreas.*—The gross changes were slight and consisted in flaccidity and dusky gray appearance, and the cut surface was often moderately bloody. Microscopically, the vascular changes were of the usual type. The cells of the acini were frequently swollen, with poor staining or faulty staining nuclei. The ductal cells presented similar changes, and occasionally were desquamated. The most important alterations were noted in the islands (Fig. 33). These were indefinitely outlined; their cells had a washed out appearance, and were poorly differentiated from one another. They were increased in size, often fragmented, and usually presented pronounced nuclear changes

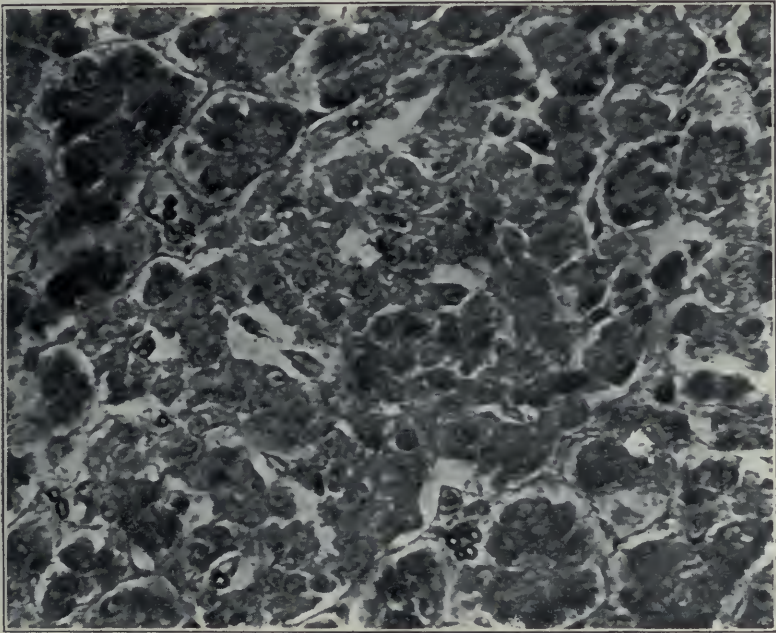


Fig. 33.—(Pancreas.) Toxic degeneration of islands of Langerhans. The islands are indistinctly outlined and consist of poorly differentiated, swollen and partly degenerated cells.

or absence of nucleus. This is a similar toxic degeneration to that observed in the liver, spleen and elsewhere.

*Mesenteric Lymph Nodes.*—The lymph nodes were moderately swollen, but never were larger than a bean. Their cut surface was slightly moist and had a grayish pink appearance. Frequently, they were definitely reddened. Microscopically, there was a slight sinus catarrh, slight lymphoid proliferation, and a moderate edema, the changes being comparable to those in the peribronchial lymph nodes, although always of a much less degree.

*Intestines.*—Practically always, larger or smaller areas of the mucosa were definitely congested and frequently submucous hemorrhages were seen (Fig. 34). The mucosa was commonly swollen, gray and turbid, and, in the duodenum, much bile stained. In the majority of instances, the lymphoid tissue was definitely hyperplastic; this condition being especially pronounced in the ileum. Of ninety-seven cases, where notes as to the lymphoid status were made, the solitary follicles and Peyer's patches were markedly hyperplastic in forty, the hyperplasia being slight, or not present, in the remaining fifty-seven instances. In the pronounced cases the follicles were swollen to the size of two or three millimeters, and usually surrounded by a definite

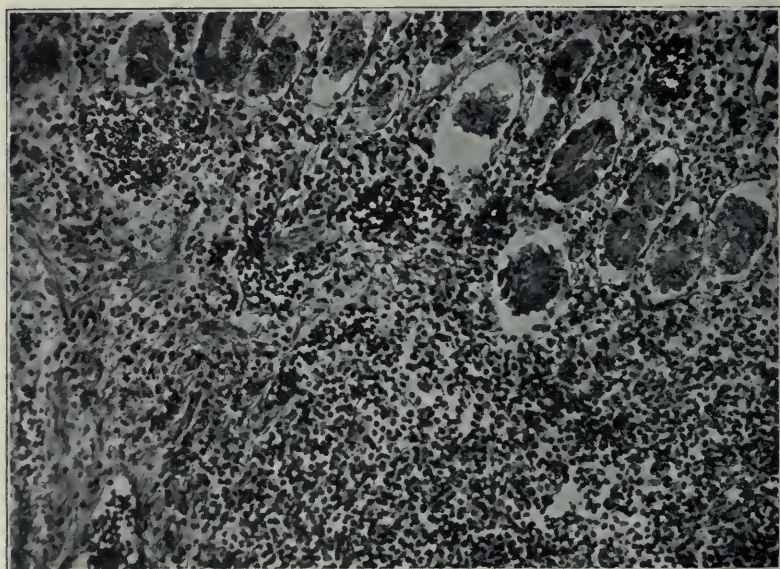


Fig. 34.—(Intestines.) Congestion and hemorrhage. Note intense congestion and areas of hemorrhage involving the mucosa and submucosa. The lymphoid tissue is proliferated.

hemorrhagic zone, giving the mucosa a coarsely granular appearance. The Peyer's patches were well raised above the surface and of a grayish brown color. Occasional central liquefaction necrosis of the follicles was encountered, resulting in the formation of vesicular structures with turbid contents. Microscopically, congestion and submucous hemorrhages were the rule. The lymphoid tissue was actively hyperplastic, presenting many large lymphoid cells and some endothelial elements. Kuskow<sup>2</sup> has observed similar changes, but believes the duodenum to be involved most often. The lymphoid hyperplasia

appears to have been much less pronounced in his cases than in our series. Hemorrhagic gastro-enteritis has been described (Juergens,<sup>49</sup> Wallis,<sup>24</sup> Windgradow<sup>50</sup>).

*Nervous System.*—The brain and its membranes were examined in eighty-five cases, and next to the diseases of the respiratory apparatus, the changes in the nervous system seem to be the most frequent and important complications in influenza.

*Dura Mater.*—Congestion, generally of a mild degree, was found in twenty-nine instances. In one case a marked internal hemorrhagic pachymeningitis occurred in conjunction with a purulent meningococcic meningitis. The entire inner surface of the dura was coated with a thick layer of firmly clotted blood, averaging from 2 to 5 mm., which adhered but slightly to the pia-arachnoid, but was firmly affixed to the dura. Kuskow<sup>2</sup> and Leichtenstern<sup>1</sup> have each reported a similar case. In a general way it may be said that the dura was much less affected than the pia-arachnoid.

*Pia-Arachnoid.*—The relative frequency of meningitis as a complication of influenzal pneumonitis is emphasized by Gmeiner,<sup>51</sup> who found it in 11 per cent. of his cases, while in ordinary croupous pneumonia it occurred in 0.5 per cent. Blanton and Irons<sup>10</sup> saw two cases of pneumococcic meningitis in their 123 postmortems. Symmers<sup>11</sup> saw one such case in twenty necropsies. Nuzum<sup>21</sup> and his associates found passive hyperemia of the pia-arachnoid and edema of the leptomeninges commonly present in their forty necropsies. Wallis,<sup>24</sup> Kuskow<sup>2</sup> and others found similar conditions. Suppurative inflammation during and after influenza was frequently observed in the military hospitals of France and Algiers by Kelsch and Antony<sup>32</sup> fifteen times in 278 cases, and Kundrat<sup>30</sup> thrice in 126 necropsies. Kuskow<sup>2</sup> found only one case of purulent meningitis. He estimates its frequency during the epidemic of 1889-1890 as from 2½ to 5 per cent., and concluded that the pia is only rarely left unchanged in influenza. Similar results could be obtained for the present epidemic (Stone and Swift,<sup>13</sup> Blanton and Irons,<sup>10</sup> Nuzum and co-workers,<sup>21</sup> Symmers,<sup>11</sup> etc.).

We found fibrinopurulent leptomeningitis thirteen times, serolymphatic meningitis, with congestion, seventeen times, and in the remaining fifty-five cases edema and congestion of more or less pronounced degree. The origin of the purulent meningitis was meningococcic in seven cases, pneumococcic in four, and streptococcic in two

49. Juergens: Berl. klin. Wchnschr. No. 10, p. 232, 1890.

50. Windgradow: Quoted by Kuskow, Footnote 2.

51. Gmeiner: Einige Beobachtungen über Influenza Während der letzten Epidemie, Prager med. Wchnschr., 1894; *ibid.* 1894.

instances. Further etiologic data will be given in the bacteriologic part of this paper. The constantly present congestion and edema doubtless created a focus of lessened resistance, explaining the frequency of meningeal complications. The frankly purulent inflammations generally occurred late in the disease, but some developed within a few days after the onset of the influenza. They differed anatomically in no way from the usual lesions of this type. The other meningeal infections which we have here termed serolymphatic appear to be the direct result of the virus of influenza. In all of these cases the membranes were soft, watery and considerably congested.

The subarachnoid fluid, especially in the large cysterns, was definitely turbid. In the sulci and surrounding the larger vessels, there

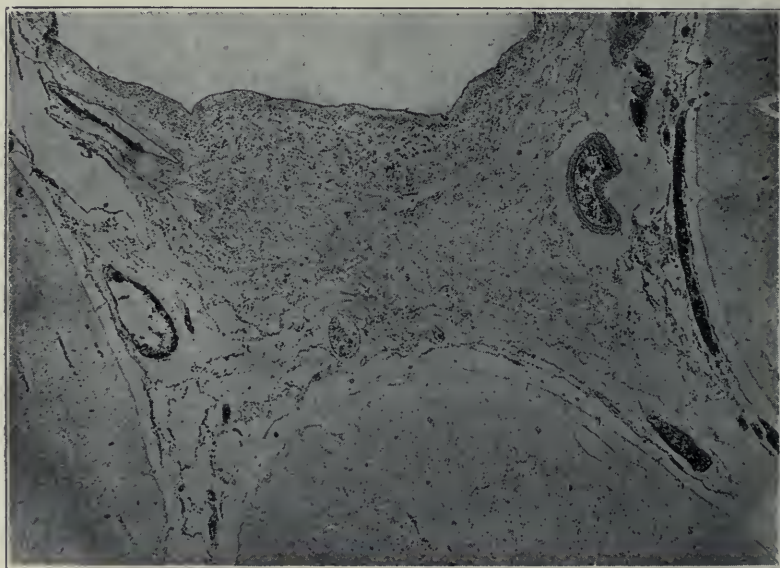


Fig. 35.—(Pia-arachnoid.) Acute serous leptomeningitis. Note distention with poorly cellular exudate and congestion. This is an early stage of the condition shown in Figure 36.

was a cloudy, turbid, grayish yellow exudate. This was most frequently observed over the temporal and parietal regions, and was slight or absent over the base of the brain. Microscopically, two types were recognized. In the first (Fig. 35) the pia-arachnoid was loosely arranged and distended with fluids, the vessels were densely filled. Isolated red blood cells and small round lymphatic cells were scattered throughout the tissue with occasional large endothelial cells. In the second type (Fig. 36) the pia-arachnoid was densely infiltrated with small round, many large, deep-staining mononuclear, some pale-staining

endothelial together with plasma cells. Polymorphonuclear leukocytes were rarely encountered, and then in small numbers; fibrin was absent, or at most only present in small traces. This type of meningitis was characterized, then, by the lymphocytic type of the cellular exudate and the scarcity or absence of polymorphonuclear cells and fibrin, together with pronounced hyperemia, edema and occasional hemorrhages.

*Brain.*—The weight of the brain was tabulated for forty-six cases. In 39 per cent. it averaged 1,300, in 50 per cent., 1,452; in 11 per cent., 1,739 gm. The weight, therefore, was increased from 100 to 200 gm. in about half of the patients. Consistency was somewhat more flaccid. The ventricles were generally of normal size, or only slightly dis-

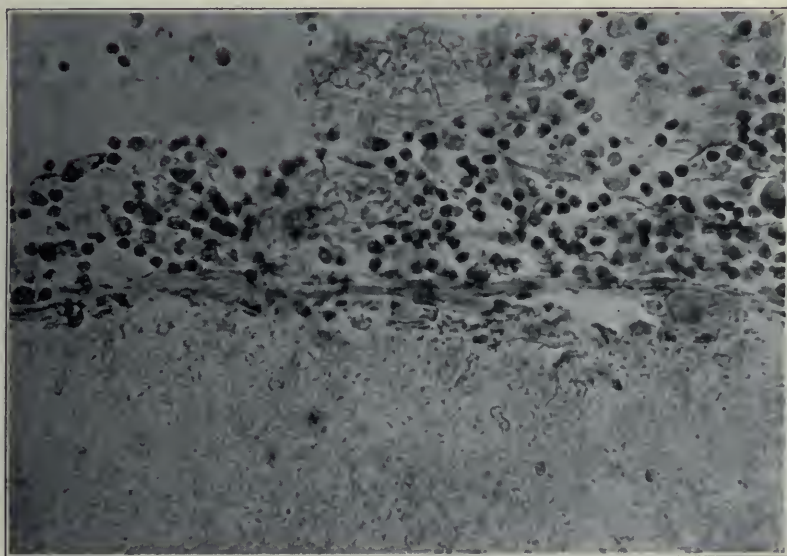


Fig. 36.—(Pia-arachnoid.) Acute serolymphatic meningitis. The exudate consists of numerous small, round cells, many large, deeply staining mononuclear cells, and plasma cells. Polymorphonuclear leukocytes are very rarely encountered, and fibrin is only present in small traces.

tended. Slight cloudiness of the ventricular fluid was often observed, even in the cases not associated with purulent meningitis. The ependyma presented no noteworthy alteration. The pineal gland was grossly normal, or at the most, somewhat softened. No microscopic studies of them are included in this series. The cut surfaces of the brain in practically every instance, presented an excessive number of bleeding points. They were most pronounced in the white matter of the hemispheres, but occasionally the corpus thalamus was especially involved. The cerebral cortex was less affected and the pons, cere-

bellum, medulla and spinal cord presented these changes in considerably less degree. These bleeding points appeared usually as closely placed, punctate, minute, hemorrhagic areas.

Microscopically, intense congestion of the vessels and numerous minute hemorrhagic foci were encountered (Fig. 37). Their distribution corresponded to the grossly hyperemic areas. The hemorrhages never exceeded, in size, the diameter of a low power microscopic field and were generally only of about half this size. The hemorrhagic encephalitis was first studied by Leichtenstern;<sup>1</sup> Schmorl<sup>52</sup> and Oberndorfer,<sup>27</sup> saw it frequently during the present European epidemic. Pick<sup>7</sup> and Leichtenstern,<sup>1</sup> occasionally found areas of hemorrhagic

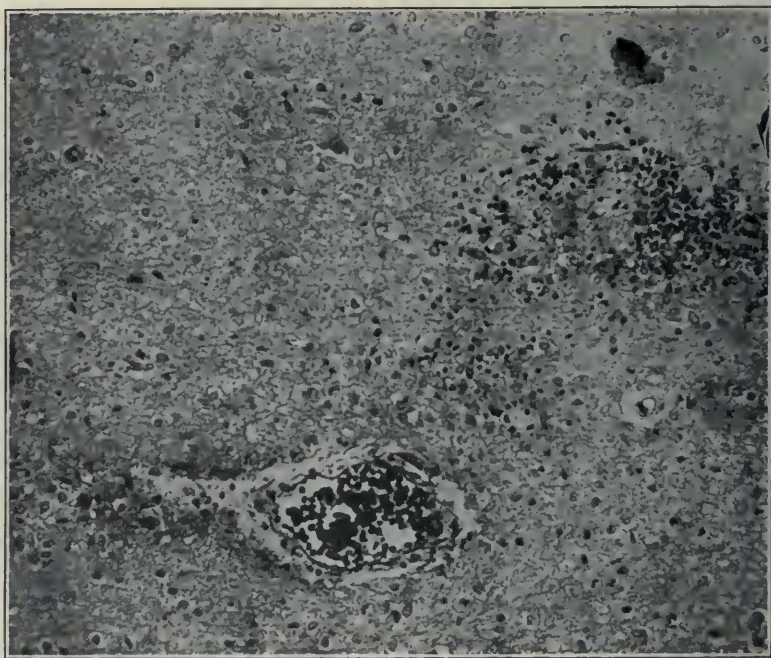


Fig. 37.—(Cerebrum.) Focal hemorrhages and congestion. Note area of hemorrhage in upper right part of photograph.

softening of considerable extent; such areas did not occur in our series. The vascular endothelium was frequently swollen and hyaline and conglutination thrombi were often met. The perivascular spaces were frequently large and contained precipitated, edematous fluid. Occasionally, only, was a perivascular cellular infiltration noted (Fig. 38). The ganglion cells presented most pronounced changes. Some-

52. Schmorl: *Path.-anat. Beobachtungen bei d. jetzt herrschenden Influenza Epidemie*, *Deutsch. med. Wchnschr.* **44**:936, 1918.

times only isolated, sometimes large groups of cells, were affected. They were generally swollen and without definite cell outline. Commonly, a small, clear, edematous zone surrounded the cells. The cytoplasm was devoid of Nissl granules and the nuclei were frequently entirely absent or showed a loss of outline. In short, all stages of cell degeneration were present, ranging from acute cloudy swelling to chromatolysis and total disappearance (Fig. 39). In no instance, however, was invasion and phagocytosis of ganglion cells observed. The glia matrix was generally arranged loosely. The cell degenerations enumerated did not appear to attack constantly any special part of the brain, and the sections of spinal cords examined were too few to formulate an opinion.

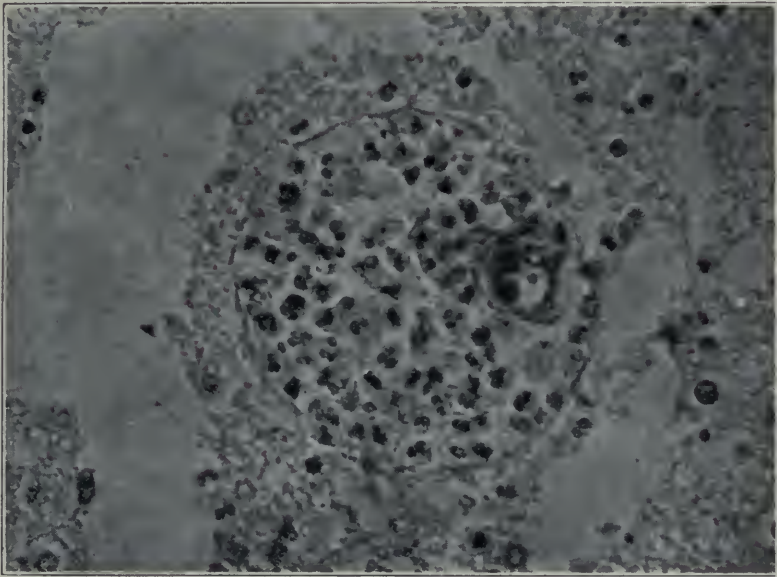


Fig. 38.—(Brain.) Perivascular cell infiltration. Note the huge distention of perivascular space with polymorphonuclear leukocytes and large mononuclear cells. The darker small circle within the polymorphonuclear mass is the vessel; the polymorphonuclear cells occupy the perivascular space. This was taken from a case of influenza complicated with suppurative meningitis. Polymorphonuclear cells are generally only met with in influenza when complications due to pus producing organism exist. Compare this with Figure 36, where the perivascular space is free from cellular contents.

*Pituitary Gland.*—This gland was only examined a few times. In each instance it was somewhat swollen, pinkish in color, the cut surface being moist, definitely bloody and reddened. Microscopically, the tubular acini were markedly distended with a colloid material, the



Fig. 39.—(Cerebrum.) Acute cloudy swelling and degeneration of ganglion cells. Note clear area of edema, surrounding ganglion cells, absence of tigroid granulation, and nuclear changes, varying from eccentric position of nucleus to partial and complete chromatolysis.

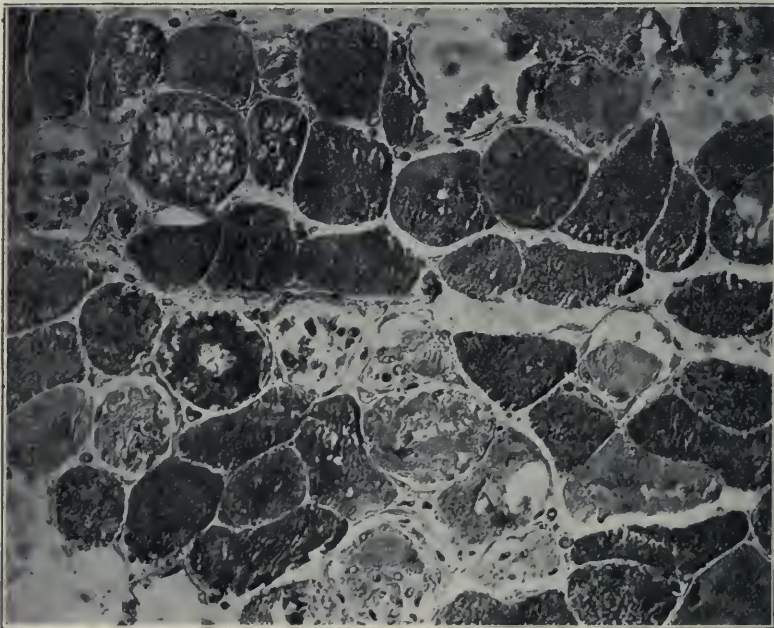


Fig. 40.—(Pituitary gland.) Hypercolloidism. Note the marked distention with colloid material.

lining cells flattened; sometimes throughout the section coarse strands of fibrin were present. The vessels were much dilated and small hemorrhages were frequently seen. The posterior lobe was unfortunately never included in the sections. These unusual findings are readily explained by the great frequency of purulent nasal sinus involvement and by the frequent association of suppurative meningitis. The section illustrated here came from a patient presenting suppuration of the sphenoid and other accessory nasal sinuses, but the meninges were not inflamed (Fig. 40).

*Special Sense Organs.*—Ear: Suppurative otitis media was present in only four instances. This stands in marked contrast to the frequency with which it occurred during a coexisting epidemic of measles where it was present in nine of twenty-five necropsied patients. During the epidemic of 1889 and the succeeding years the relative infrequency of middle ear involvement was noted. Thus, the Swiss Commission<sup>53</sup> found it in only 2 per cent. of 1,508 cases. Leichtenstern<sup>1</sup> gives similar figures.

Eye: Hyperemia and inflammation of the conjunctiva were very frequently found and would probably indicate the generalized vascular engorgement rather than a localized condition. No microscopic sections of the eyes were made.

#### CHRONIC INFLUENZA

While influenza, as a rule, runs an acute course, it may become protracted over a considerable period. This condition has been especially studied by Lord,<sup>54</sup> Filatoff,<sup>55</sup> Franke<sup>56</sup> and others. Any case of influenza which extends over a period of four weeks or more, generally with remittent or intermittent fever, and various lung symptoms, may be looked on as typical of the chronic form of this disease. The authors mentioned, and others, state that clinically such a condition often resembles typhoid, malaria, tuberculosis, or low grade septicemia. These "subacute and chronic nontuberculous pulmonary infections" have lately been reviewed by Miller.<sup>57</sup>

Five patients of our series of 126 presented this condition. The duration of the disease varied from 44 to 88 days, with an average of 60 days. Judging from the clinical records, each patient suffered with

53. Swiss Commission: Quoted by Leichtenstern, Footnote 1.

54. Lord, F. T.: Boston M. & S. J. **147**:662, 1902; *ibid.* **153**:537, 1905.

55. Pilatoff, N.: Ueber Protrahierte u. Chron. form d. influenza, Arch. f. Kinderheilk. **27**: 1889.

56. Franke, Felix: Ueber Chronische Influenza, Beihefte zur med. Klin., Berlin **5**: 1909.

57. Miller, Alexander: Subacute and Chronic Nontuberculous Pulmonary Infections, Am. J. M. Sc. **154**:805, 1917.

an initial typical attack of influenza, which was followed, sooner or later, by signs of pneumonic consolidation and accompanied throughout by a fluctuating fever curve. The pneumonitis seemed to persist, but shifted from place to place, constantly involving new areas, while the older pneumonic patches persisted or sometimes cleared up.

All these cases came to necropsy during the last period of the epidemic, or rather after the bulk of the epidemic had subsided. They showed certain anatomic differences which justify their separate discussion.

There was emaciation in each instance, two showed slight icterus, none the intense cyanosis and lividity so commonly seen in the acute cases. The cut surface of the subcutaneous tissues and muscles was never so bloody and moist as in the acute disease. In one instance a large abscess in the rectus muscle was present. Acute purulent peritonitis occurred thrice, which is in marked contrast to its absence in the acute cases of our series. The changes in the aorta and other vessels were similar but more profound.

*Pericardium and Heart.*—Purulent pericarditis, associated with a purulent inflammation of the other serous membranes, was present once. In the rest no noteworthy changes were found. There was particularly an absence of subserous, hemorrhagic extravasations and of hyperemia.

The heart varied in weight from 205 to 425 gm., with an average of 310 gm. The right heart was constantly dilated, and in one instance both chambers were markedly dilated. The muscle was always very flaccid, light grayish red and turbid.

Microscopically, there was shown marked swelling and vacuolization of hydropic character, and while the vessels were not congested, usually they contained hyaline thrombi, which were more pronounced in the chronic than in the acute cases. Endothelial hyperplasia varied in degree in the chronic form, and no definite comparative picture could be formed.

*Respiratory Tract.*—The peribronchial lymph nodes were always greatly swollen, soft and edematous, but only slightly congested. Microscopic section presented edema, sinus catarrh, slight connective tissue proliferation, and, in two instances, an acute purulent adenitis, with the presence of large numbers of polymorphonuclear leukocytes and small areas of necrosis. The vessels showed no other changes than those mentioned above.

The trachea and bronchi possessed a relatively pale mucosa which was covered in every instance with mucopus; in the smaller branches a thick, creamy, yellow pus was present. Microscopically, well marked

erosion of the wall, and the presence of enormous numbers of polymorphonuclear cells characterized the picture. Bronchiectasis never occurred, although commonly seen in chronic influenza.

The pleurae, in each instance, were adherent in places by relatively firm, fibrous bands and by more recent fibrinous exudate. This seemed to have persisted for some time, since it was generally rather tough. The pneumonic process, according to the records, varied in duration from twenty-seven to seventy-four days with an average of 44.1 days. The lungs were never so voluminous as in the acute type, and in no instance exceeded the volume usually seen in a chronic bronchopneumonia, the left lung averaging 440, the right 480 gm. in weight. Slaty blue, sometimes depressed, firm areas could be felt, especially on the posterior border in either lung. The cut surface was only slightly bloody, and in every instance the interpulmonary septa were prominent and there were larger and smaller areas of fleshy appearance and consistency. Soft, grayish brown foci, finely and coarsely granular, apparently recent consolidations, and smooth, velvety, firm areas could be seen, but in general the extent of pulmonary involvement was less than in the acute cases.

Microscopically, certain characteristic features were always present; namely, areas of atelectasis, sometimes of considerable extent; areas of young connective tissue overgrowth (carnification) and areas of necrosis and abscess formation. All stages of pneumonic involvement could be observed in the sections from these lungs. In every instance small, bronchopneumonic patches, with fibrinocatarrhal exudate of recent origin, were found. Generally, however, the exudate consisted of polymorphonuclear leukocytes, with little or no fibrin; the alveolar walls were infiltrated in places with such cells, and were frequently destroyed, resulting in abscesses which often reached considerable dimensions. The perivascular and peribronchial tissues were often definitely fibrous. In one instance a pronounced hyperplasia of epithelium, similar to that described in acute cases, was encountered.

*Spleen.*—The spleen varied in weight from 105 to 260 gm., with an average of 185 gm.; on the whole, the organ was therefore smaller than in the acute cases. The capsule was generally wrinkled; the color of the organ was a reddish gray; the consistency was always flaccid, but never soft or mushy. The cut surface was only slightly bloody; trabeculae could generally be seen, but were not thickened. In one case the follicles were prominent, in the others indistinct.

Microscopically, there was a distinct hyperplasia of endothelial cells throughout the organ; in two instances large numbers of polymorphonuclear leukocytes were present. Fibrosis of the reticulum was noted

twice. Definite toxic hyaline degeneration of the arterial walls was noted in another case. Areas of hemorrhage were seen twice.

*Suprarenals and Semilunar Ganglia.*—Slight congestion and edema were observed. In one instance there was infiltration of the adrenal with polynuclear leukocytes, otherwise the changes were similar to those previously described.

*Kidneys.*—Twice the kidneys were below average weight, and three times increased in size and weight, the average for the series being 193 gm. for the left and 190 gm. for the right kidney. In two cases the capsule was slightly adherent, tearing the parenchyma on stripping. The consistency in every instance was flaccid; the cut surface was pale, swollen and reddish gray, with poor differentiation of cortex and medulla. Cortical and medullary markings had a washed-out appearance. Hemorrhagic exudates in the renal pelvis were never observed.

Microscopically, there was a slight edema and congestion present in all, but no connective tissue overgrowth. The glomerular and tubular changes were similar to those described, differing only in greater degree of severity. In one instance polymorphonuclear leukocytes in large numbers were present in the glomerular capillaries; in another case the capsular epithelium was slightly proliferated. The tubular epithelium was considerably more degenerated than in the acute cases; many tubules were lined with entirely necrotic cells.

*Liver.*—Two cases were below the average in weight (1,330 gm.), the other three averaged 2,270 gm. The consistency was flaccid in each instance, the lower border well rounded. The color was generally grayish brown. The cut surface was slightly bloody, lobulation was indistinct, but sometimes the centers of the lobules were large and deep red.

Microscopically, the two small livers presented marked degeneration of cells, areas of focal necrosis and a diffuse infiltration of polymorphonuclear cells which latter was somewhat more marked in the periportal tissue. In the other organs varying degrees of cloudy swelling were observed.

*Meninges and Brain.*—The dura mater presented no changes. The pia-arachnoid was twice slightly edematous, and in one case of the three examined the vessels were considerably congested. Much opacity was present in this case, and over the superior surface of the cerebellum there was a small amount of grayish yellow exudate. This patient had shown symptoms of spinal meningitis for about one month, but repeated lumbar punctures failed to bring out the causative organism.

Microscopically, there was a round cell infiltration with few leukocytes and some fibrin. The brain weight in the three cases averaged 1,480 gm. Only once did the cut surface show the marked congestion and petechial hemorrhage described above, while in the other two no gross changes were noted. Microscopically, there were degenerative changes in the ganglion cells similar to those already described; hemorrhages were never found.

#### SUMMARY

The influenza pandemic of 1918 manifested itself at Camp Zachary Taylor and Camp Knox, Kentucky, Sept. 22, 1918, and terminated about November 15. One hundred and twenty-six definitely proven cases of influenza, occurring in previous healthy soldiers of approximately the same age and physical condition, were chosen for this study. One hundred and twenty-one of these cases represented the acute, five the chronic type of the disease. All stages of the epidemic are covered. Routine bacteriologic cultures were made in every instance.

Considerable discrepancy was found in the morbidity and mortality rates between white and negro soldiers, the incidence of influenza being considerably less among the colored soldiers, while their mortality was higher.

The average duration of life was found to be fourteen days; about 50 per cent. of the patients died within ten days. There was a tendency for the duration of the disease to increase as the epidemic progressed.

The external appearance of the necropsied cases usually presented an extreme lividity. Expansion of the chest was frequently found.

*Skin.*—Two types of skin lesions were encountered. These were purpura hemorrhagica, in about 20 per cent., and toxic necrosis of the sebaceous follicles in about 60 per cent. of the cases. Jaundice was present in about 10 per cent.

*Subcutaneous Tissues.*—Generalized emphysema was present in three cases. We believe the mode of origin of this to lie in ulcerative or erosive bronchiectasis with escape of the air in the peribronchial tissue and thence to the mediastinum and subcutaneous tissue.

*Muscles.*—Zenker's hyaline degeneration of the rectus muscles was observed in about 10 per cent. of the cases. Acute myositis occurred once. Abscesses occurred once each in the acute and chronic cases.

*Peritoneum.*—Peritonitis occurred in none of the acute and three times in the chronic cases.

*Blood Vascular System.*—Extreme congestion, areas of hemorrhages, conglutination and hyaline thrombosis, and swelling of the

vascular endothelium was commonly present. Rarely was a toxic hyaline degeneration of the arterial wall seen. Polymorphonuclear leukocytes were only found in complicating suppurative processes; their absence seemed to indicate a myeloid intoxication. Lymphoid hyperplasia was, on the other hand, often very pronounced.

*Aorta.*—Slight acute atheroma was present in about 85 per cent. of the cases; diffuse hemoglobin tinting of the intima was frequently observed.

*Pericardium.*—Pericarditis occurred seven times. Punctate hemorrhagic extravasations and hyperemia were common.

*Heart.*—The heart muscle was practically always affected. In over 90 per cent. of the cases more or less relaxation of the right heart was present; in over 80 per cent. an associated cloudy swelling occurred. Microscopically, there was an acute parenchymatous degeneration and vacuolization. Endocarditis was seen only once.

*Respiratory System.*—The respiratory mucosa was generally somewhat swollen and frequently hemorrhagic. The accessory nasal sinuses presented purulent or sanguinopurulent involvement in about 85 per cent. of the cases. The peribronchial lymph nodes were generally congested, enlarged and edematous. Microscopically, an acute sinus catarrh was almost always present. The larynx was involved in about one-third of our cases, while the trachea and bronchi presented a hemorrhagic or catarrhal mucosa in almost every instance. Ulcerative and purulent bronchiolitis was very common.

*Pleurae.*—The pleurae were involved on one or both sides in over 80 per cent. of the cases. The exudate was generally slight in amount, frequently hemorrhagic and usually poor in fibrin. Analysis in reference to the duration of the disease and period of epidemic brought out the fact that purulent and the more pronounced fibrinous fluids occurred at a later stage of the epidemic. Petechial subpleural hemorrhages were very frequent.

*Lungs.*—Pneumonitis developed usually early. All but two cases presented pneumonic involvement, but the amount of lung involvement was occasionally so slight that it was evidently not the cause of death. In over 90 per cent. of the cases both lungs were involved. The lung was generally much above normal weight. The pneumonitis was generally lobular in type, true croupous lobar pneumonia occurring in only thirteen instances. In seven of these it formed the only type of pulmonary consolidation; in six others it was associated with bronchopneumonia. The bronchopneumonic areas varied considerably in texture, color and consistency, were usually poorly circumscribed, and tended to become confluent. The upper lobe was almost as frequently

affected as the lower. The nonconsolidated lung tissue was generally very hyperemic. Microscopically, three types of exudates were differentiated: catarrhal, fibrinocatarrhal, and fibrinopurulent. All of these often occurred within the same lung, or even in the same microscopic section. The catarrhal types of exudates appeared to be primarily produced by the virus of influenza, while the fibrinous and purulent types were probably the results of secondary and tertiary invading organisms. The essential pathology of true influenzal pneumonitis seemed to be the extreme hyperplasia of the pulmonary epithelium, but since invading organisms were generally abundant a mixed catarrhal, fibrinous and suppurative pneumonitis was generally encountered.

*Spleen.*—The spleen was definitely enlarged in over 80 per cent. of the cases and considerably enlarged in 30 per cent. It was usually flaccid, occasionally mushy and generally bloody. Trabeculae were rarely recognized distinctly. Follicular enlargement was uncommon. Necrosis of the reticulum, endothelial hyperplasia, and toxic hyaline degeneration of arterial walls and germinal centers were frequently found.

*Semilunar Ganglia.*—Marked changes in the ganglion cells, varying from cloudy swelling to complete disappearance were prominent. Hyperemia was usually present.

*Suprarenals.*—The adrenals were usually congested and somewhat edematous, and in three cases a frank hemorrhage was present. Lipoid exhaustion was the most notable change.

*Kidneys.*—The kidneys were generally enlarged, flaccid and congested. The tubular lumen and capsular spaces contained abundant granular precipitate. The tubular epithelium was degenerated and sometimes necrotic. Proliferation of the capsular epithelium occurred occasionally. The kidney changes seemed to be in the nature of a parenchymatous degeneration with edema rather than of a productive nephritis.

The genital organs were frequently congested. Cellular degeneration and absence of spermatogenesis were commonly found.

*Upper Gastro-Intestinal Tract.*—Submucous hemorrhages were frequent. A moderate lymphoid hyperplasia was present.

*Liver.*—The liver was definitely increased in size and weight in over 90 per cent. Cloudy swelling, with various stages of congestion, were common. Focal necrosis was present in about 50 per cent. of the cases. In one instance a true acute yellow atrophy was encountered, and in several more necrotic changes which could be looked on as precursors of yellow atrophy.

*Pancreas.*—Toxic degeneration of the islands of Langerhans occurred with great frequency.

*Intestines.*—The solitary follicles and Peyer's patches were as a rule definitely enlarged. Congestion and submucous hemorrhages were often found.

*Brain Membranes.*—The dura mater was congested in about one-third of the cases. Once a marked internal hemorrhagic pachymeningitis occurred. The pia-arachnoid was practically always involved. Suppurative meningitis, due to secondary invaders, was present in 20 per cent. A serolymphatic leptomeningitis, characterized by a slight exudate of cells belonging to the lymphocytic type and by absence of polynuclear cells and fibrin, was encountered in one-third of the cases. Edema and hyperemia were practically always present.

*Brain.*—The brain was generally congested, hyperemia and focal hemorrhages being very frequent. Degeneration of ganglion cells was pronounced. The changes were more marked in the cerebrum, while the cerebellum, medulla, pons and spinal cord showed relatively slight alterations.

*Pituitary.*—A marked hypercolloidism was observed. Fibrinous inflammation, extending from the neighboring suppurating sinuses, occurred.

*Ear.*—Suppurative otitis media was present in only 3 per cent. of the cases. Bone necrosis was not observed.

*Eye.*—Hyperemia and conjunctivitis were common.

#### CHRONIC INFLUENZA

In five of our cases the duration of the disease averaged sixty days. These were regarded as cases of chronic influenza and presented certain characteristic features. All of the patients were markedly emaciated. The intense postmortem lividity encountered in the acute cases was absent. The serous membranes were frequently involved. Thus, pericarditis was present in one case, and peritonitis in three instances, with a partially organized pleural exudate in every case. The organs generally presented more pronounced parenchymatous degenerations, but hemorrhages and marked congestions were absent. The heart always showed cloudy swelling and hydropic degeneration. The lungs evidenced pneumonic processes of long standing, the average duration being forty-four days. Fibrosis, carnification, atelectasis and abscesses were common, but there were always recent fibrinocatarrhal areas. The spleen was generally smaller than in acute cases, and in two instances contained large numbers of polynuclear cells. The changes in the suprarenals and semilunar ganglia were similar to those encoun-

tered in acute cases. The kidneys presented pronounced glomerular tubular nephritis. In two instances an acute suppurative hepatitis with numerous focal necroses was present. Meninges and brain showed degenerative changes similar to those found in the acute cases, but the vascular changes were slight.

#### BACTERIOLOGIC PART

From the inception of the epidemic at Camp Zachary Taylor it was our routine to take cultures from the principal tissues at each necropsy—heart's blood, pericardium, right and left pleurae, right and left lungs (all lobes), spleen, bronchial exudate, nasal accessory sinuses, sub-arachnoid space and ventricles, and elsewhere as occasion demanded.

Besides cultures, routine smears were made to act as a check on cultural findings. In our charts only cultural readings have been submitted, and this has undoubtedly lowered some percentages, but it did not seem fair to report only on staining affinity and morphologic grounds.

The reports, both pathologic and bacteriologic, of the present pandemic, as shown in the literature to date, reveal such an appalling divergency in conclusions, such diversity in reading results and in the means employed to get those results, that we are constrained to analyze our findings in comparison with those from cases not to be considered as due in any degree to the prevailing epidemic, in order to see if there were not some underlying principles governing what appeared to be a disordered mélange in the organisms found.

As a preliminary it would seem fair to state what is meant when we say we have found a particular organism. The necessity for this is shown by the fact that certain observers have regarded as pneumococci, organisms which are gram-positive diplococci whether bile soluble or not, and some have typed with pneumococcic antisera bile insoluble organisms. In this series we regarded the bile solubility test as final; a diplococcus or diplostreptococcus, whether capsulated or not, whether lanceolate or not, if bile insoluble was regarded as a streptococcus, either hemolytic or nonhemolytic according to a predetermined estimate of hemolysing ability. Frequently we encountered pneumococci agglutinating with two or more of our type antisera; these were properly regarded as Type IV. Some observers have reported the absence of the *B. influenzae*, and in their culture media they have taken no regard of its hemophilic propensities; the criteria we have demanded are mentioned below.

The gradations between hemolytic and nonhemolytic streptococci are so fine and indistinct that we had to adopt a standard of differentiation and arbitrarily chose the ability of an 18 hours' broth culture

to produce hemolysis with equal parts of a 5 per cent. sheep suspension in the water bath at 37.5 C. for two hours. The amount of the hemolysis, whether complete or not, was not considered. Some strains would give complete hemolysis in half an hour or less, while others would not cause complete hemolysis in the two hours, but an evident hemolysis, however slight, at the end of our time period was sufficient to enable us to make a differentiation. All tests were run with two saline controls. The hemolytic streptococci were again subdivided in a number of instances by the Holman<sup>58</sup> sugar standard. By this means we determined the curious fact that *S. pyogenes*, which had so abounded at Camp Zachary Taylor in 1917-1918 (reports by Lucke and Rea,<sup>59</sup> and by Alexander,<sup>60</sup> Camp Taylor) is not represented among those found this year, its place being taken by hemolytic streptococcus No. 2. Double tests with fresh sugars were taken and corroborated these findings. Fifty strains of streptococcus were examined with the following results:

Hemolytic streptococcus:	Per cent.
No. 2 .....	70.3
No. 1 .....	3.7
No. 3 .....	7.4
Equinus .....	11.2
Infrequens .....	7.4
Nonhemolytic streptococcus:	Per cent.
Equinus .....	45.5
Ignavius .....	22.7
No. 2 .....	11.3
Mitior .....	11.3
Salivarius .....	11.3

This hemolytic streptococcus No. 2 was very frequently gram-negative, not taking the Gram stain after repeated cultivation. It was recovered at one time or another from practically every organ or tissue, and on two occasions from the spinal fluid.

By the *B. influenzae* we mean a minute organism, gram-negative, pleomorphic, hemophilic, which would not grow at room temperature, or only very slightly, and was generally killed by icebox temperature. As a medium we used for a time rabbits' blood glycerin agar, the growth appearing as multitudinous dewdrop colonies in from 20 to 48 hours. With the Washington formula the colonies were much larger, ringed and diverse in size and contour, giving a false impression of contamination. More latterly we have used Avery's<sup>61</sup> oleate

58. Holman, W. L.: The Classification of Streptococci, J. M. Res. **34**:377 (July) 1916.

59. Lucke, Baldwin, and Rea, Marion: Hemolytic Streptococci, etc., J. Infect. Dis., 25, May, 1919.

60. Alexander, H. L.: Hemolytic Streptococcus Causing Severe Infections at Camp Zachary Taylor, Ky., J. A. M. A. **70**:775 (March 16) 1918.

61. Avery, Oswald T.: J. A. M. A. **71**:2051 (Dec. 21) 1918.

medium with very gratifying results. Agglutination experiments of our cultures against serum from recovered cases were doubtful or unsuccessful, except in two instances where we get the following results after incubation at 55 C. for eighteen hours followed by twelve hours in the icebox:

1:2	1:10	1:20	1:40	1:80
++	++	++	+	±

Under the head of *Micrococcus catarrhalis* we include all members of this group, hardly any attempt at sugar or other differentiation having been made in the time at our disposal. Latterly, though, we have found a prevalent diplococcus, both in sputum and at necropsy, the colonies resembling the *Micrococcus catarrhalis*, but morphologically showing slight differences. Since it fermented dextrose, saccharose and lactose we have considered the possibility of it being *Micrococcus crassus*.

With these preliminary explanations we here submit our charts.

TABLE 8.—COMPARATIVE INCIDENCE OF BACTERIAL FLORA IN ONE OR MORE ORGANS OF 120 NECROPSIES OF INFLUENZA, AND 101 OTHER ACUTE DISEASES OCCURRING DURING THE INFLUENZA EPIDEMIC

	Heart's Blood				All Organs			
	Influenza (107)		All Other Diseases (101)		Influenza (120)		All Other Diseases (101)	
	Num-ber	Per Cent.	Num-ber	Per Cent.	Num-ber	Per Cent.	Num-ber	Per Cent.
<i>B. influenzae</i> .....	30	28.0	4	3.9	74	61.6	22	21.7
Hemolytic streptococcus..	32	29.9	32	31.6	41	34.1	51	50.4
Nonhemolytic strept. ....	31	28.9	10	9.9	56	46.6	18	17.8
Pneumococci (typed).....	24	22.4	5	4.9	43	35.8	11	10.8
Pneumococci (untyped)...	6	5.6	5	4.9	25	20.8	12	11.8
<i>M. catarrhalis</i> .....	3	2.8	1	0.9	35	29.1	11	1.1
Meningococcus.....	0	0.0	0	0.0	2	1.6	4	3.9
<i>M. tetragenus</i> .....	0	0.0	1	0.9	6	5.0	2	1.9
Staphylococcus.....	2	1.8	5	4.9	18	15.0	30	29.7
Diphtheroids.....	0	0.0	0	0.0	6	5.0	0	0.0

In Table 8 we make a comparison of the bacterial findings from 120 influenzal with those from 101 necropsies from other causes. These deaths all occurred during the period under consideration and should give a fair line, if such is to be obtained, on the leading bacterial factors in the epidemic seen at Camp Zachary Taylor. It will be seen that four organisms especially predominated in the influenza cases; these were *B. influenzae*, a nonhemolytic streptococcus, pneumococcus of the various types, and *M. catarrhalis*.

The presence of the Pfeiffer bacillus in the heart's blood of 3.9 per cent. of the noninfluenza cases is to be explained by the fact that there

was a concurrent epidemic of measles, and these cases in a high percentage carried an organism indistinguishable from the *B. influenzae*, judging from a series of nasopharyngeal swabbings. The hemolytic streptococcus was not found in so high a percentage as in the non-influenzal cases, and it was only at the latter end of the epidemic, and in those cases which were protracted, that it was met with to any considerable extent; so that we have been inclined to look on it as a tertiary invader, in view of the fact that it has been endemic in this camp for the past eighteen months. The other organisms mentioned on this chart need not now be considered.

The outstanding prominence of the *B. influenzae* is very noteworthy, and when the difficulty of its isolation and the fact that in the long continued cases it seems to have died out or been replaced by the secondary or tertiary invaders, it is evident that these figures can only represent the minimum number of times it was present during some period of the disease. In only two of our series did we have a pure infection with this organism, and these were very early in the epidemic. Early also were eight cases of mixed infection with *B. influenzae* and a nonhemolytic streptococcus, and three of *B. influenzae* pneumococcus; eight cases scattered throughout the epidemic of pure nonhemolytic streptococcus. Midway was one of pure *M. catarrhalis*; ten cases mostly at the very end of pure hemolytic streptococcus, and eight cases in this last period of mixed hemolytic streptococcus and staphylococcus. Nonhemolytic streptococcus and pneumococcus were found about three times as often in the influenza as in the noninfluenza cases. *M. catarrhalis* was very prominent in the latter part of the middle of the epidemic.

One very interesting organism encountered was a small biflagellated protozoon, measuring from 5 to 8 microns, and without undulating membrane, tentatively assigned to the *Prowazekia*. This was discovered in three cases close together toward the middle of the epidemic. In one instance it was recovered from the heart's blood; in another from the sphenoid sinus, and in the third from the left lung. A later notice on this organism will be issued when it has been more thoroughly studied.

Table 9 gives the incidence and distribution of the bacteria according to the period of the epidemic. We have divided the epidemic into four time periods, the dates being given in Table 2, except that periods 4 and 5 of this table are consolidated here and constitute period 4 in Table 9. For sufficient reason we have amalgamated the readings of the right and left pleurae, right and left lungs, the accessory nasal sinuses and mastoid cells. By "other structures" are meant liver,



peritoneum, gallbladder, skin, enteric follicles, or whatever tissue seemed to us to be worthy of examination outside of those adopted as routine. This table points out forcibly (a) the gradual lowering in the incidence rate of *B. influenzae*, nonhemolytic streptococcus and pneumococcus; (b) the sudden rise into prominence in the third period of the *M. catarrhalis*, and (c) the remarkable manner in which the hemolytic streptococcus and the staphylococcus came to the fore in the last period. The latter especially had been practically nonexistent, so far as our necropsy cultures showed during the first three periods. The sudden recurrence of *B. influenzae* in the fourth period will be discussed later.

Table 10 shows the incidence of the bacteria in the various organs. In this table is given in brackets the actual number of times each organism was found, also the resulting percentage per number of examinations made. Here again we see that the trinity, *B. influenzae*, nonhemolytic streptococcus and pneumococcus were the predominating findings in all the tissues examined. The high percentage of hemolytic streptococcus is due in most part to the very considerable frequency with which it appeared in the fourth period as above pointed out. Type IV, as elsewhere, was the principal pneumococcus found, followed by considerably less than half that number of Types IIa and II, which were almost equal in point of frequency. In this table the figures for the heart's blood are based on the total number of cultures taken, and not excluding the hopelessly contaminated, thirteen in number. If these last be taken into account, a slight increase in all the percentages would have to be recorded.

It is in line with the pathologic picture revealed at necropsy that the findings for the subarachnoid and brain ventricles were so frequently positive.

Table 11 divides our findings according to a different method; that is, according to the time the disease lasted before a fatal termination. Detailed figures have already been given in showing the relation of duration of disease to period of epidemic. Naturally, those that endured the longest came to necropsy in the later periods; so that there must necessarily be some similarity between this and the preceding table. But this table shows most forcibly the gradual disappearance of the *B. influenzae* in the longest enduring cases and the encroachment of the hemolytic streptococcus in the same. The relative infrequency of the hemolytic streptococcus in the bronchial exudate as compared with its appearance in the lungs may be due to the fact that so many more lung examinations were made, especially as toward the end of the epidemic examination of the bronchial exudate was discontinued, and at this time the hemolytic streptococcus flourished most vigorously.

TABLE 10.—INCIDENCE OF BACTERIA IN THE VARIOUS ORGANS

	Organs								
	Heart's Blood	Pleurae Right 41 Left 43	Lungs Right 116 Left 117	Bron- chial Exudate	Spleen	Subtrach- noid and Brain Ventricles	Accessory Nasal Sinuses and Mastoid Cells	Other Structures	Total
Number of organs examined.....	(120) %	(84) %	(233) %	(51) %	(110) %	(68) %	(99) %	(53) %	(818) %
<i>B. influenzae</i> .....	(30) 25.0	(13) 15.4	(74) 31.7	(22) 43.1	(25) 92.7	(7) 10.2	(28) 98.8	(13) 24.5	(212)
Hemolytic streptococcus.....	(31) 25.8	(21) 25.0	(65) 27.8	(9) 17.6	(14) 12.7	(6) 8.7	(13) 13.1	(9) 16.9	(168)
Nonhemolytic streptococcus.....	(31) 25.8	(26) 30.9	(65) 36.4	(18) 35.2	(21) 19.0	(15) 22.0	(33) 33.3	(7) 13.2	(296)
<i>Pneumococcus</i> , Type I.....	(3) 2.5	(2) 2.3	(10) 4.2	(2) 3.9	(3) 2.7	(0) 0	(2) 2.0	(1) 1.8	(23)
<i>Pneumococcus</i> , Type II.....	(5) 4.1	(3) 3.5	(12) 5.1	(1) 1.9	(3) 2.7	(4) 5.8	(3) 3.0	(1) 1.8	(33)
<i>Pneumococcus</i> , Type IIa.....	(4) 3.3	(6) 7.1	(8) 3.4	(4) 7.8	(3) 2.7	(3) 4.3	(6) 6.0	(3) 5.6	(37)
<i>Pneumococcus</i> , Type III.....	(2) 1.6	(0) 0	(6) 2.5	(1) 1.9	(1) 0.9	(3) 4.3	(2) 2.0	(0) 0	(15)
<i>Pneumococcus</i> , Type IV.....	(9) 7.5	(9) 10.7	(25) 10.7	(10) 19.6	(6) 5.5	(6) 8.7	(15) 15.1	(2) 3.7	(82)
<i>Pneumococcus</i> , untyped.....	(6) 5.0	(7) 8.3	(24) 10.3	(4) 7.8	(2) 1.8	(3) 4.3	(11) 11.1	(3) 5.6	(60)
<i>M. catarrhalis</i> .....	(3) 2.5	(3) 3.5	(34) 14.5	(9) 17.6	(6) 5.5	(1) 1.4	(5) 5.0	(4) 7.5	(65)
<i>Meningococcus</i> .....	(1) 0.8	(0) 0	(0) 0	(0) 0	(0) 0	(2) 2.9	(2) 2.0	(0) 0	(5)
Diphtheroids.....	(3) 2.5	(0) 0	(6) 2.5	(4) 7.8	(2) 1.8	(0) 0	(0) 0	(0) 0	(15)
<i>Staphylococcus</i> .....	(4) 3.3	(2) 3.3	(18) 7.5	(1) 1.9	(5) 4.5	(2) 2.9	(2) 2.0	(1) 1.8	(35)
<i>M. tetragenus</i> ....	(0) 0	(1) 1.1	(2) 0.8	(1) 1.9	(0) 0	(0) 0	(1) 1.0	(0) 0	(5)
Total number organisms found.....	(132)	(92)	(369)	(86)	(91)	(52)	(125)	(44)	(991)

TABLE 11.—DISTRIBUTION AND INCIDENCE OF BACTERIA PRESENT ACCORDING TO DURATION OF DISEASE (IN PER CENT.)

	Organs										Other Structures				
	Heart's Blood		Pleurae		Lungs		Bronchial Exudate		Spleen		Subarachnoid and Brain Ventricles	Accessory Nasal Sinuses and Mastoid Cells		Duration of Disease in Days—	
	Duration of Disease in Days—	1 6 11 16 to to to to	Duration of Disease in Days—	1 6 11 16 to to to to	Duration of Disease in Days—	1 6 11 16 to to to to	Duration of Disease in Days—	1 6 11 16 to to to to	Duration of Disease in Days—	1 6 11 16 to to to to		Duration of Disease in Days—	1 6 11 16 to to to to		
Number examined..	8 49 24 26		10 48 17 15		16 98 60 60		3 34 16 10		2 47 28 31		4 23 25 20		4 32 30 47		2 11 6 20
B. influenzae..	25.0 36.7 29.1 11.5		10.0 18.7 29.4 0		25.0 45.9 23.3 18.3		33.3 26.4 56.2 30.0		100.0 34.0 17.5 6.4		0 8.6 8.0 10.0		25.0 18.7 46.6 14.9		50.0 27.2 66.6 5.0
Hemolytic streptococcus..	0 28.5 3.7 34.6		0 31.2 29.4 26.6		0 32.6 29.6 30.0		0 11.7 18.7 0		0 19.1 17.5 9.6		0 13.0 4.0 15.0		0 15.6 16.6 6.3		0 9.0 16.6 30.0
Nonhem. streptococcus....	25.0 30.6 29.1 34.6		10.0 25.0 35.2 46.6		56.2 36.7 35.0 25.0		33.3 14.6 50.0 40.0		50.0 17.0 21.4 16.1		25.0 26.0 24.0 25.0		75.0 3.4 36.6 14.9		0 27.2 33.3 5.0
Pneumococcus, Type I....	0 0 1.2 0		0 2.0 5.8 0		12.5 1.0 8.3 0		0 2.9 0 0		0 2.1 7.1 0		0 0 8.0 0		0 0 3.3 0		0 0 0 0
Pneumococcus, Type II....	0 4.0 8.3 3.8		0 2.0 5.8 0		0 6.1 6.6 3.3		0 0 6.2 0		0 0 0 0		0 0 12.0 0		0 0 6.6 4.2		0 0 33.3 0
Pneumococcus, Type III....	12.5 4.0 4.1 0		10.0 8.3 5.8 0		12.5 3.0 5.0 0		33.3 2.9 12.5 0		0 2.1 3.5 3.2		25.0 0 12.0 0		25.0 9.3 6.6 0		0 0 33.3 0
Pneumococcus, Type IV....	0 2.0 0 3.8		0 0 0 0		0 5.1 0 3.3		0 0 10.0 0		0 2.1 0 0		0 8.6 0 5.0		0 3.1 0 2.1		0 0 0 5.0
Pneumococcus, untyped....	12.5 4.0 8.3 19.2		10.0 2.0 11.7 13.3		12.5 5.1 8.3 21.6		33.3 2.9 12.5 40.0		50.0 4.2 3.5 3.2		0 4.3 0 15.0		0 9.3 23.3 10.6		0 0 0 0
Pneumococcus, total.....	37.5 20.1 21.9 34.4		50.0 20.5 40.8 13.3		56.2 38.6 33.2 33.2		66.6 20.4 49.9 80.0		50.0 16.8 14.1 6.4		25.0 17.2 36.0 20.0		25.0 31.0 49.7 21.1		50.0 9.0 16.6 5.0
M. catarrhalis.....	0 0 4.1 7.6		20.0 0 5.8 0		37.5 11.2 6.6 15.0		33.3 5.8 18.7 20.0		0 2.1 0 16.1		0 0 4.0 10.0		0 6.2 0 6.3		50.0 9.0 16.6 5.0
Meningococcus.....	0 0 0 0		0 0 0 0		0 0 0 0		0 0 0 0		0 0 0 0		0 0 8.0 0		0 0 0 0		0 0 0 0
M. tetragenus.....	0 0 0 0		10.0 0 0 0		0 2.0 0 0		0 0 6.2 0		0 0 0 0		0 0 0 5.0		0 0 0 0		0 0 16.6 0
Diphtheroids.....	0 0 4.1 3.8		0 0 0 0		0 1.0 5.0 3.3		0 2.9 12.5 10.0		0 4.2 0 3.2		0 0 0 5.0		0 0 0 0		0 9.0 0 0
Staphylococcus.....	0 0 4.1 3.8		0 0 0 0		12.5 8.1 3.3 11.6		0 0 0 10.0		50.0 2.1 0 3.2		0 4.3 0 0		0 3.1 0 4.2		0 0 0 5.0

Early in October, 1918, the sputum of 129 influenza patients was examined (Table 12). It will be seen that in the early days the hemolytic streptococcus was not very prominent, showing in 5 per cent., whereas the trinity of *B. influenzae*, nonhemolytic streptococcus and pneumococcus, and of those typed, Type IV constituted 76.9 per cent., were very much the most prominent organisms. One hundred and fifty other sputums sent to the laboratory routinely during October and November show *B. influenzae* 9.4 per cent., and hemolytic streptococcus in 33 per cent., indicating how much oftener hemolytic streptococcus was generally found than in the actual influenza cases.

TABLE 12.—SPUTUM EXAMINATION FROM INFLUENZA PATIENTS DURING OCTOBER, 1918 \*

Total examinations, 729 Organisms	Number	Per Cent.
<i>B. influenzae</i> .....	315	43.2
Hemolytic streptococcus.....	39	5.3
Nonhemolytic streptococcus.....	309	42.3
Pneumococcus, Type I.....	7	13.4
Pneumococcus, Type II.....	2	3.8
Pneumococcus, Type III.....	3	5.7
Pneumococcus, Type IV.....	40	76.9
Unsuitable for typing.....	447	61.3
Pneumococcus, total.....	499	68.4
Staphylococcus.....	191	26.2
<i>M. catarrhalis</i> .....	99	13.5
<i>M. tetragenus</i> .....	5	0.7

\* In the great majority of instances these sputums were unsuitable for type determination, being thin and unwashable. Also they were taken in such quantities and in so brief a time that with the force at our command we could only select the best specimens which showed as nearly as possible pure culture.

TABLE 13.—INCIDENCE OF ORGANISMS IN THROATS OF 250 CASES OF INFLUENZA (FIRST TEN DAYS OF EPIDEMIC, FROM SEPTEMBER 21 TO OCTOBER 1)

	Number	Per Cent.
<i>B. influenzae</i> .....	45	18.0
Hemolytic streptococcus.....	13	5.2
Nonhemolytic streptococcus.....	76	30.4
<i>M. catarrhalis</i> .....	82	32.8
Staphylococcus.....	43	17.2
Pneumococcus.....	44	17.6

In the very first ten days of the epidemic (from September 21 to October 1) swabbings from the throats of 250 influenza cases were taken (Table 13). It is remarkable how closely the findings simulate those of the sputum from the same class of patients taken during the ensuing ten days or so. Here again the hemolytic streptococcus was found in only 5 per cent., while nonhemolytic streptococcus, *M. catarrhalis* and *B. influenzae* together with pneumococcus and staphylococcus in lesser degree were the most prominent. In other words, the organ-

isms which we consider to be most responsible are most evident even in the initial swabbings before the epidemic had broken in its full fury upon us.

It is interesting to note from our records that in two months—January and February—following the epidemic, 178 sputum examinations were made with the following findings:

Pneumococcus .....	71.9 per cent.
Hemolytic streptococcus .....	33.4 per cent.
Nonhemolytic streptococcus .....	30.8 per cent.
<i>Bacillus influenzae</i> .....	6.7 per cent.
Staphylococcus .....	45.5 per cent.
<i>Micrococcus catarrhalis</i> .....	58.9 per cent.

One hundred and sixteen pneumococci were typed as follows:

Type I .....	1 case
Type II .....	4 cases
Type IIa .....	0 case
Type III .....	3 cases
Type IV .....	108 cases
Untyped .....	12 cases

Thirty-three necropsies for the same period showed:

	Heart's Blood, No. Cases	Lungs, No. Cases	Spleen, No. Cases	Pleural Cavities, No. Cases
Pneumococcus .....	2	3	0	1
Hemolytic streptococcus .....	17	22	12	9
Nonhemolytic streptococcus .....	5	5	0	0
<i>B. influenzae</i> .....	1	1	0	0
Staphylococcus .....	2	4	0	1
<i>Micrococcus catarrhalis</i> .....	1	3	1	1

These last are very interesting as showing the extraordinary pre-dominance of hemolytic streptococcus to the exclusion of the main factors during the epidemic. As regards the overwhelming preponderance of Type IV pneumococcus in these more recent sputum examinations, it should be remembered first, the liability to salivary contamination, and second, in the present wave of enthusiasm for type determination of pneumococcus we are unconsciously subscribing to the premise that it alone, when present, is responsible for the pathologic condition, often overlooking entirely the more dangerous cohabitant. It is worthy of note, too, how the *B. influenzae* has almost disappeared from both necropsy and sputum findings. It should be remarked that these latter statistics contain a very few cases of undoubted influenza, so the presence of bacillus of Pfeiffer in small percentages is agreeably accounted for.

Lastly, we come to the consideration of five cases which lasted forty days or more. In every one of these cases hemolytic streptococcus was the offending organism. In four cases it was recovered

from the heart's blood. In one it was associated with *M. catarrhalis* in the left lung. But with this exception they were all five pure hemolytic streptococcus infections. This bears out our contention that hemolytic streptococcus was a tertiary invader, and by its luxuriant growth supplanted the original organisms.

#### SUMMARY AND DISCUSSION

While no attempt has been made to collect all the bacteriologic literature it seems desirable to review a number of the reports on the present pandemic for purposes of comparison. The previous great pandemic has been so ably presented by Kolle and Wassermann<sup>62</sup> that we may well omit it from our present discussion. Selter,<sup>63</sup> of Königsburg, experimenting on himself and a woman assistant, Nicolle and LeBailly,<sup>64</sup> and later Rivi  re,<sup>65</sup> Gibson and Connor<sup>66</sup> published results which would seem to suggest the possibility of a filtrable virus, but their findings are not altogether identical and are contradicted in their entirety by the experiments of Rosenau and Keegan<sup>67</sup> on nine volunteers from the Deer Island Naval Station, men who had not previously been exposed to the disease, and therefore were eminently suitable subjects. The experiments on a much larger body of men at San Francisco,<sup>68</sup> men who had previously been inoculated with a protective vaccine of *B. influenzae*, pneumococcus and streptococcus, were likewise entirely negative. Further contradiction is furnished by the negative results of Nuzum et al.<sup>21</sup> at the Cook County Hospital.

On the other hand, Keegan<sup>67</sup> recovered the *B. influenzae* in a series of twenty-three necropsies, from the lungs in 82.6 per cent. of the cases, in 31.6 per cent. of which it was in pure culture. In our series it was recovered pure from both lungs in two cases, and these were early in the epidemic. In both these cases it was recovered from the heart's blood and all other organs examined with positive results, viz., spleen and pericardium.

62. Kolle and Wassermann Handbuch d. pathogenen Mikroorganism, Jena, Gustav Fischer, 1914.

63. Selter, H.: Zur Aetiologie der Influenza, Deutsch. med. Wchnschr. **43**: 932, 1917. Quoted by British Research Committee.

64. Nicolle, C., and LeBailly, C.: Quelques notions Exp  rimentales sur le virus de la Grippe, Compt. rend. Acad. d. sc., **167**:607, 1918.

65. Dugarric de la Riv  re, R.: La Grippe, est elle une Maladie    virus filtrans? Compt. rend. Acad. de sc. **167**:606, 1918.

66. Gibson, and Connor, J. I.: Filtrable Virus as Cause of Early Stage of Present Epidemic of Influenza, Brit. M. J. **2**:645 (Dec. 14) 1918. Etiology of Influenza, Brit. M. J. **2**:331 (March 22) 1919.

67. Keegan: The Prevailing Pandemic of Influenza, J. A. M. A. **71**:1051 (Sept. 28) 1918.

68. U. S. Navy at San Francisco: Some Interesting, Though Unsuccessful. Attempts to Transmit Influenza Experimentally, Pub. Health Rep. **34**:33, 1919.

The Conference of Bacteriologists at the British War Office under Col. Sir William Leishman,<sup>69</sup> while not altogether satisfied as to the primary etiologic significance of *B. influenzae*, had no doubts as to its frequent presence in the epidemic and the great importance of the part it played in the production of symptoms and complications. Synnott and Clark<sup>70</sup> from Camp Dix report, "Bacillus of Pfeiffer has been encountered in the majority of cases *when looked for*." "It has been recovered from the lung substance, the bronchi, the trachea and sputum, but from none of over 300 blood cultures." "In no case was it the sole invading organism . . ." "Whatever rôle *B. influenzae* plays in the present epidemic it does not invade the blood, and in all probability cannot solely be responsible for the fatal termination . . ." with most of which, with the modification that it can and does invade the blood and is capable alone of forming a fatal pneumonitis, we are in accord.

Hall, Stone et al.<sup>29</sup> reporting seventy-nine uncomplicated cases of influenza, found in the sputum the following: *B. influenzae* fifty-eight times, pneumococcus seventy-six times, *M. catarrhalis* thirty-nine times, hemolytic streptococcus four times and in nine necropsies they recovered from the lungs: Pneumococcus four times, *B. influenzae* once, hemolytic streptococcus once, and had negative results thrice. Their sputum and throat findings are similar to our own in that they show the relative infrequency of the hemolytic streptococcus. It is surprising that the nonhemolytic streptococcus was not reported at all, and we are inclined to wonder if it has been included under the head of pneumococcus, as has been done in other reports, notably that of Keegan<sup>68</sup> who places his reliance on morphology, thus, no doubt, including as Type IV pneumococcus many such organisms as in our report are set down as nonhemolytic streptococcus. Blanton and Irons,<sup>10</sup> in reporting the bacteriology of heart's blood and lungs in 280 pneumonitis cases at necropsy, recovered the hemolytic streptococcus more frequently than the nonhemolytic streptococcus, lungs 76.66 and heart's blood 64:48; respectively; *B. influenzae* was recovered eight times from the lungs and twice was the sole organism present. In the heart's blood it was found three times, once alone. Here we have three cases of pure influenzal pneumonitis, as against our two. Their streptococci sugar reactions are in no wise comparable with ours, as they did not find any mannite fermenters.

69. London Letter: Quoted in J. A. M. A. **71**:1759 (Nov. 23) 1918.

70. Synnott, M. J., and Clark, E.: Influenza Epidemic at Camp Dix, J. A. M. A. **71**:1816 (Nov. 30) 1918.

The experiments of Julia Parker<sup>71</sup> would seem to indicate that the *B. influenzae* excretes a filtrable exotoxin, and if confirmed, constitute a very valuable addition to our knowledge. Stone and Swift,<sup>13</sup> at Fort Riley, implicate *B. influenzae* or an unknown virus as the etiologically responsible agent. The experiences of Base Hospital No. 17,<sup>72</sup> in France, indicated the primary importance of the Pfeiffer bacillus in this epidemic, as do editorials in the *British Medical Journal*.<sup>73</sup> Averill, Young and Griffiths,<sup>74</sup> in a report before the Medical Research Committee of Great Britain, gave 75 per cent. *B. influenzae* in forty-three cases; pneumococci also constituted 75 per cent. of the findings. Dietrich and Neisser<sup>75</sup> found *B. influenzae* in 100 per cent. of seven necropsies. The Budapest Clinic<sup>76</sup> claims to have isolated the bacillus of Pfeiffer from every case examined. Rapoport<sup>77</sup> found *B. influenzae* in over 80 per cent. of his necropsies and showed the presence of antibodies in 54.5 per cent. out of 295 convalescents, whereas, of 300 control serums only 9.6 per cent. fixed complement. These figures, if confirmed, are a strong argument in favor of those who still believe that the Pfeiffer bacillus is the prime causal agent. Stillman and Pritchett,<sup>78</sup> using Avery's<sup>58</sup> oleate medium, cultivated *B. influenzae* in 93 per cent. of cases of influenza and bronchopneumonitis. Incidentally, they also recovered it in 43 per cent. of normal individuals. In uncomplicated influenza it was recovered in 83 per cent. of forty-nine cases; in influenza with bronchopneumonia, in 93 per cent. of forty-three cases; in bronchopneumonia in 100 per cent. of six cases, and in lobar pneumonia in 55 per cent. of twenty cases. The Kitasato Institute<sup>79</sup> considers *B. influenzae* the cause of the pandemic. They found the bacillus of Pfeiffer in pure culture in the nasal cavities of patients. Hicks and Gray,<sup>80</sup> too, encountered the *B. influenzae* in high percentage in their series of cases—80 per cent. in the nasopharynx and 75 per cent. in the sputum.

71. Parker, Julia: A Filtrable Poison Produced by Bacillus Influenza (Pfeiffer), J. A. M. A. **72**:476 (Feb. 15) 1919.

72. Weekly Bulletin, A. E. F., No. 27, 1918.

73. Brit. M. J. Editorials **2**: Paragraphs 39 and 91, 1918.

74. Averill, Young, Griffiths: The Influenza Epidemic in a Camp, Brit. M. J. **2**:111 (Aug. 3) 1918.

75. Dietrich, A.: Pathologische-anatomische Beobachtungen über Influenza im Felde, München. med. Wchnschr. **65**:928, 1918. Quoted by Brit. Med. Res. Committee.

76. Quotation from Report of Brit. Med. Res. Committee.

77. Rapoport, F. H.: The Complement Fixation Test in Influenzal Pneumonia, J. A. M. A. **72**:633 (March 1) 1919.

78. Stillman and Pritchett: J. Exper. M. **29**:259 (March) 1919.

79. Okawara, I., Tanaka, T., et al.: Kitasato Arch. Exper. Med., **2**:235, 1918.

80. Hicks, A. B., and Gray, L.: Influenza in Woolwich District, Lancet **2**:419, 1919

So far the evidence implicating the bacillus of Pfeiffer has been very strong. On the other hand, Bircher<sup>81</sup> indicates streptococcus. Uhlenhuth<sup>82</sup> only made cultural recovery of *B. influenzae* in 13 per cent. of his sputums, and once he found it in an empyema and a throat swab. His blood cultures were negative. Rosenow<sup>83</sup> found the green producing lanceolate diplostreptococcus, for which Tunnicliff<sup>84</sup> finds increased opsonic content in the serum of recovered cases. Stitt<sup>85</sup> failed to find antibodies for various strains of *B. influenzae*, and from Camp Fremont, Brem<sup>86</sup> et al., while frequently finding *B. influenzae*, consider an ultramicroscopic filtrable virus to be the responsible agent, with as secondary complicating organisms, the hemolytic streptococcus, the nonhemolytic streptococcus, Type IV pneumococcus, and, in bronchopneumonia, *B. influenzae*. Ely, Lloyd et al.<sup>87</sup> consider the hemolytic streptococcus to be the cause, for in twenty postmortems they found the hemolytic streptococcus in the heart's blood seventeen times. Their findings would agree with ours in the latest periods of the epidemic, and in the long protracted cases where *B. influenzae* had died out or been replaced. Pfeiffer<sup>88</sup> reports findings of his bacillus inconstant. MacCallum<sup>44</sup> considers that in some regions *B. influenzae* was a particularly common secondary invader, in others it was insignificant. But, apparently, he has not considered the time period at which the investigations were made. Simmonds<sup>89</sup> found it in both sputum and postmortem material "very frequently." He also reports secondary streptococcic infection to be more common than in the pandemic of 1890.

Taking a few consecutive cases at any one period of the epidemic as manifested here, we could reproduce the exact picture as reported from any one of the above quoted observers. In the early days we

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81. Bircher, E.: Influenza Epidemic, Corr.-Bl. f. Schweiz. Aerzte **48**:1338, 1918.

82. Uhlenhuth: Zur Bakteriologie der Influenza, Med. Klin. **14**:777, 1918. Quoted by Brit. Med. Res. Committee.

83. Rosenow, E. C.: Prophylactic Inoculation Against Respiratory Infections, J. A. M. A. **72**:31 (Jan. 4) 1919.

84. Tunnicliff, Ruth: Phagocytic Experiments in Influenza, J. A. M. A. **71**:1733 (Nov. 23) 1918.

85. Stitt, E. R.: American Public Health Association. Quoted in J. A. M. A. **71**:2098 (Dec. 21) 1918.

86. Brem, W. V., Bolling, G. E., Caspar, E. J.: Pandemic Influenza and Secondary Pneumonia at Camp Fremont, Calif., J. A. M. A. **71**:2138 (Dec. 28) 1918.

87. Ely, C. F., Lloyd, B. J., Hitchcock, C. D., Nickson, O. H.: Influenza at Puget Sound Navy Yard, J. A. M. A. **72**:24 (Jan. 4) 1919.

88. Pfeiffer: Quoted by Brit. Med. Res. Committee.

89. Simmonds, M.: Zur Pathologie der diesjährigen Grippe, München. med. Wchnschr. **65**:873, 1918.

were discussing the predominance of the bacillus of Pfeiffer or the nonhemolytic streptococcus, the latter gathering strength as the former subsided (Table 9). Then as these in turn slowly dwindled, *Micrococcus catarrhalis* began to attain some prominence in the third period, followed in the fourth by an explosion of hemolytic streptococcus and staphylococcus. There is a rather curious flurry in the fourth period, i. e., the appearance of *B. influenzae* in the heart's blood of eight of thirty-three cases. We explain this by the fact that there were several fulminating cases at that time, which also coincided with the height of the epidemic in the neighboring town of Louisville, Ky. Of the fifty-seven cases of less than ten days' duration, while the majority fell in the earliest part of the epidemic, a large minority appeared in the fourth period, and in these the original invaders were not supplanted by the tertiary organisms, hemolytic streptococcus and staphylococcus, so common at that time.

Our sputum charts, submitted above, give added force to the necropsy picture. It must be remembered that our methods and media were the same at the beginning of the epidemic as they had been during the previous winter of 1917-1918, and yet, the Pfeiffer organism had only rarely been encountered. With the coming of the epidemic came also this organism, in large amount at first, and then as our cultural methods and media were improved to meet the situation, it began to decline in frequency of appearance unto almost the vanishing point. It is our belief that if we had the Avery<sup>61</sup> oleate medium in the last days of September, 1918, our findings in this respect would have easily been doubled.

#### CONCLUSION

1. The incidence of influenza is greater among whites than among negroes, but the mortality rate is higher among the latter.
2. The average duration of life is fourteen days; in the early part of the epidemic the average duration of life is considerably shorter, and in the latter part considerably longer.
3. The anatomic and bacteriologic findings vary with the stage of the epidemic and of the disease, and depend to a certain extent on the endemic bacterial flora. Earlier in the epidemic the disease was more fulminating, and during this time the *Bacillus influenzae* was most often found; as the epidemic progressed and the attacks lengthened, secondary invaders appeared more and more frequently and corresponding anatomical changes were found.
4. Influenza produces widespread changes throughout the body, and while the lungs commonly present the most spectacular lesions,

pronounced alterations are also encountered in the nervous, cardiovascular and other systems.

5. The most general changes produced by influenza are pronounced congestions, hemorrhages, toxic degenerative lesions and hemorrhagic inflammations. Hyperemia and hemorrhages are especially striking in the meninges, brain, serous membranes (petechial hemorrhages), skin (intense cyanosis, purpura hemorrhagica), lungs, spleen, liver and kidneys. Examples of toxic degenerations are Zenker's hyaline degeneration of the rectus muscles, conglutination and hyaline thrombosis, hyaline degeneration of vascular walls, hyaline degeneration of germinal centers of splenic follicles, focal necrosis of the liver, pancreas and suprarenal, toxic ganglionic changes and edema in the nervous system, and cloudy swelling of parenchymatous organs. Hemorrhagic inflammations are exemplified in early pneumonitis and pachymeningitis; productive inflammations are uncommon and confined to the later stages of the disease.

6. The true pneumonitis of influenza is characterized by extreme proliferation of pulmonary epithelium, pronounced hyperemia and hemorrhages. The commonly present secondary invaders produced a pneumonitis which grossly and microscopically consists of a number of separate, dissimilar pathologic processes. Macroscopically, a lobular pneumonia, with a tendency to become pseudolobar, and with a mixed, smooth and granular cut surface, is present. Microscopically, there are four distinct types of exudates, often within the same microscopic section, but distinctly independent. These are: catarrhal, fibrino-catarrhal, fibrinopurulent and purulent in type.

7. Throughout the disease there is a relative paucity of polymorphonuclear leukocytes and a proliferation of the lymphoid tissue; this would seem to point to myeloid intoxication and to lymphoid stimulation.

8. Chronic influenza is characterized by relative absence of vascular changes, connective tissue proliferation and diffuse suppuration.

9. The influenza bacillus, although not found in every case, was present in a sufficiently high percentage, and often enough in acute fatally ending infections to consider it, if not the prime cause, at least the most important indicator of epidemic influenza. At all events its appearance with the epidemic and its relative absence prior thereto, using the same cultural methods, strongly strengthens the assumption of its pathogenic rôle.

10. *Bacillus influenzae* was easily cultivated early in the epidemic and during the recrudescence of the last period, and this corresponded with the fulminating pathology of these stages.

11. As the patients lived longer and the epidemic progressed, bacterial agents, well established at this post as the cause of respiratory tract disease, notably the nonhemolytic streptococcus and pneumococcus, appeared as secondary invaders and modified the bacterial readings and anatomic changes.

12. The nonhemolytic streptococcus, it should be stated, was a frequent commensal in the earliest part of the outbreak.

13. It is noteworthy that all the above secondary invaders were more fatal in symbiosis than alone.

14. Later in the epidemic the hemolytic streptococcus assumed the ascendancy, as a tertiary invader crowding out the secondary invaders, and was of especial importance in cases of long duration. Staphylococcus and *M. catarrhalis* made their appearance toward the end of the epidemic and to some extent modified the pathology.

We wish to enter a plea for the reading and recording of total bacterial flora and their symbiotic relationships; by this means too great weight would not be placed on single observations, like typing of pneumococci. Furthermore, in the study of this disease, observation should be made on the stage of the epidemic and the individual cases. By this method the proper relations of the various organisms can be calculated.

We wish to express our grateful appreciation for the constant advice and constructive criticisms of Major Herbert Fox, Chief of the Laboratory Service, at whose request the writers pursued this investigation. To Dr. Fred Weidman, of the University of Pennsylvania, our thanks are due for the considerable pains he took in photographing our material.

## A STUDY OF THE INCIDENCE OF PULMONARY TUBERCULOSIS IN SOLDIERS WITH IRRITABLE HEART \*

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There is a superficial resemblance between the symptoms of "irritable heart of soldiers" and those of active pulmonary tuberculosis. Ready fatigue, breathlessness, tendency to excessive sweating, tachycardia, and symptoms of asthenia are common to the two conditions. Pain in the left chest, however, which is one of the commonest symptoms of irritable heart, is not characteristic of pulmonary tuberculosis. In the careful study of the history of men with irritable heart, a background of neurotic symptoms, neurologic disease, mental inferiority, emotional instability or psychic maladjustments is almost invariably discovered. Such conditions are, of course, not characteristic of pulmonary tuberculosis.

In a recent report, Warfield and Smith<sup>1</sup> found evidences of pulmonary tuberculosis in a large number of men with the diagnosis of irritable heart or some other synonym of "soldiers' heart." In 235 cases of irritable heart, pulmonary tuberculosis was found in eighty-eight. In forty-one cases, exercise brought out positive chest findings and rise of temperature, and the authors felt that, had intensive study of the whole group been possible, the incidence of pulmonary tuberculosis would have been larger.

This report calls attention to the important fact that before the diagnosis of irritable heart can be made, a careful general examination must be done in order to determine whether the symptoms can be explained by any existing organic disease. The diagnosis of irritable heart must be made largely by excluding certain other conditions; the two conditions that are probably most important are hyperthyroidism and pulmonary tuberculosis. It should be possible, especially with the diagnostic accessories of a hospital, to sort out cases of active tuberculosis of the lungs with a fair degree of accuracy.

After this preliminary sorting out of organic disease, however, there remains the group of men with the symptom complex of irritable heart and no demonstrable organic disease. This group is represented

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\* This work was done under the direction of Capt. Bertnard Smith in the general study of Irritable Heart at U. S. Army General Hospital No. 9, Lakewood, N. J.

1. J. A. M. A. **71**:1815 (Nov. 30), 1918.

in Warfield and Smith's report by 147 men in whom tuberculosis was not found; no evidence is brought to show that tuberculosis plays any rôle in producing the symptoms of which these men complain.

On hypothetical grounds one might explain some of the symptoms of irritable heart by inferring or assuming the presence of healed or latent pulmonary tuberculosis. Extensive fibroid changes in the lungs might produce breathlessness and fatigue; the other symptoms would be more difficult to explain on this basis. It seems unlikely that pulmonary lesions of extent sufficient to cause the symptoms of irritable heart would elude careful physical examination, but it is conceivable, and this report is made with the purpose of contributing some observations on this subject.

At General Hospital No. 9, 246 cases of irritable heart have been studied. A careful history and physical examination was made in each case, directed, not only toward the cardiac condition, but toward the general condition of the patient as well. Each of these men was under observation for a period of weeks. During this time, they were given graded physical exercises, and temperature readings were made regularly. As the result of such observations, no man was found to have active pulmonary tuberculosis on admission. Two men with active lesions were admitted to the cardiac service of this hospital, but both happened to have organic heart disease.

*Effect of Influenza.*—Among the group of soldiers believed to have irritable heart, two developed active pulmonary tuberculosis following influenza. Both these men had been under observation for tuberculosis, as one of them had tuberculous glands of the neck and the other had had a recent pleurisy. Neither of these men showed symptoms, physical signs, or fever suggesting pulmonary tuberculosis until after influenza, when they developed typical symptoms and signs. The assumption in connection with these two cases is that the influenza caused activation of a tuberculous focus that had escaped detection before the acute infection. It is not, however, safe to infer that pulmonary tuberculosis was the cause of these men's complaints before the influenza. Influenza is a severe pulmonary infection, and one that is likely to attack the integrity of the lungs in a very searching manner, and the tuberculosis that follows it might arise in a small and previously healed focus. Influenza attacked thirty-seven other men with irritable heart, all of whom made an uneventful recovery.

It has been said that pulmonary tuberculosis in the active stage was found in no patient sent into the cardiac wards of this hospital with irritable heart. Healed tuberculosis of the lungs was found in one case. In this case, the diagnosis was made by both physical examination and

# FINDINGS OF HISTORY, PHYSICAL AND ROENTGEN-RAY EXAMINATION

Name	Family and Past History	Physical Examination	Roentgenogram of Lungs
C. E. ....	One sister died of pleurisy	Negative for tuberculosis	Few calcifications at hilums, otherwise negative
C. C. ....	Negative	Negative for tuberculosis	Some calcified glands at hilums; slight infiltration; negative for tuberculosis
F. J. ....	Negative	Negative for tuberculosis	Negative
F. J. ....	Negative	Negative for tuberculosis	Hilus thickening; apices clear
G. G. ....	Grandfather, maternal grandmother and 1 aunt died of tuberculosis	Negative for tuberculosis	Few calcified glands at right hilus; otherwise negative
H. E. ....	Negative	Negative for tuberculosis	Negative
L. W. ....	One brother had tuberculosis (doubtful); never ill, except acute bronchitis 1 yr. prior; now has chronic cough, mucus expectoration, at times bloodstreaked	No abnormal findings	Calcified glands at hilums; considerable peribronchial thickening, extending to periphery in right lower lobe, up to clavicle on right; probably not tuberculosis
L. W. ....	Negative	Negative	Normal peribronchial thickening; no tuberculosis
L. S. ....	Negative	Negative for tuberculosis	Negative
M. J. ....	Negative	Negative for tuberculosis	Peribronchial shadows right lower lobe; negative for tuberculosis
M. R. ....	Negative	Negative for tuberculosis	Calcified glands right hilus; pleural thickening right base; negative for tuberculosis
M. A. ....	Negative	Negative for tuberculosis	Negative for tuberculosis
M. H. ....	Negative	Negative for tuberculosis	Peribronchial shadows right lower lobe; negative for tuberculosis
M. W. ....	Negative	Negative for tuberculosis	Some peribronchial thickening; negative for tuberculosis
M. ....	Negative	Negative for tuberculosis	Peribronchial thickening right lower lobe; not reaching to diaphragm; negative for tuberculosis
T. P. ....	Negative	Negative for tuberculosis	Bronchial shadows right lower lobe, not tuberculous
T. W. ....	Negative	Negative for tuberculosis	Slight thickening of both hilums; negative for tuberculosis
H. H. ....	Negative	Negative for tuberculosis	Some peribronchial thickening, especially in bases, following influenza; negative for tuberculosis
W. E. ....	Negative	Negative for tuberculosis	Slight hilus thickening; no tuberculosis
G. M. ....	Negative	Negative for tuberculosis	Hilus thickening; negative for tuberculosis
S. S. ....	Father died tuberculosis; 1 brother has tuberculosis; past history negative.	Negative for tuberculosis	Slight bronchial thickening, extending to clavicle on right; negative for tuberculosis
C. ....	Negative	Negative for tuberculosis	Considerable peribronchial thickening, extending to periphery. No spotty infiltration; negative for tuberculosis
H. ....	Negative	Negative for tuberculosis	Not done
M. ....	Not obtained	Negative for tuberculosis	Hilums thickened; negative for tuberculosis
W. ....	Negative	Negative for tuberculosis	Slight infiltration, especially of right base; negative for tuberculosis
W. ....	Negative for tuberculosis	Signs of tuberculosis, pulmonary, chronic, inactive, right upper lobe	Marked thickening about roots of both lungs, and extension from hilus to middle of left lung. Apices clear; spotty infiltration up to clavicle on right; probably old tuberculosis
Mc. ....	Negative	Negative	Flat plate: slight thickening of hilums; negative for tuberculosis; stereoscopic plates: slight spotty infiltration of both apices, possibly tuberculosis
Z. ....	Family history negative; doubtful hemoptysis 6 mos. prior; dry cough for past 4 mos., following gassing	Negative	Some bronchial infiltration of both lungs, not tuberculous
R. ....	Negative for tuberculosis	Negative	Some bronchial thickening, extending up to clavicles, probably not tuberculous
C. ....	Incomplete	Negative	Negative
LeC. ....	Negative	Negative	Negative
M. ....	Father died of pulmonary tuberculosis; history otherwise negative for tuberculosis	Negative	Negative

roentgenogram. This case happens to be included in the group described in the table, of men who were studied more carefully than was customary.

An unselected group of men with irritable heart was studied especially for indication of pulmonary tuberculosis. The results are shown in the table. The history consisted in inquiry for tuberculosis in the family, and for hemoptysis, chronic cough, loss of weight, pleurisy and so forth in past life. The physical examination consisted of careful examination of the lungs, including auscultation after cough.

Major J. Woods Price of Saranac made fourteen of the physical examinations tabulated above while on a visit to this hospital, and he has kindly consented to allow his findings to be incorporated. Stereoscopic roentgenograms were made in twenty-nine cases, flat plates in three. Lieuts. M. H. Glover and W. A. Newell have generously given their time for careful examination of these plates for tuberculosis. Five plates were also examined by Major Price.

Only one man showed evidence of pulmonary tuberculosis by physical examination; this consisted of a healed lesion at the right upper lobe. The roentgenogram in this case also showed tuberculous changes. Even counting this case, it is doubtful whether a group of healthy individuals would show any less evidence of tuberculosis than did these men with "irritable heart."

*Summary.*—1. In a group of 246 men with "irritable heart of soldiers" studied at this hospital, one was found with definite signs of arrested pulmonary tuberculosis. Two men of this group developed active pulmonary tuberculosis after influenza. No other diagnosis of pulmonary tuberculosis was made.

2. Intensive study of thirty-two cases of irritable heart showed arrested pulmonary tuberculosis in only one case, with no instance of active tuberculosis.

#### CONCLUSION

No evidence has been found, from the study of irritable heart at this hospital, that there exists more than an accidental relationship between this condition and pulmonary tuberculosis.

## THE INCREASE OF EXTRACT NITROGEN IN THE TISSUES, WITH CHRONIC NEPHRITIS \*

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It has been well established that one of the characteristic features of one type of chronic nephritis is the retention of nitrogen. This has been demonstrated in a number of different ways, beginning with the observation of Bright that there was an increase of urea in the blood. Modern methods have elaborated on the original findings and in recent years metabolic studies of these cases have shown a positive balance between intake and output of nitrogen. I have reported studies of this kind, demonstrating that with certain cases the retention may be more than one gram of nitrogen a day, when the protein intake is equivalent to 10 gm. of nitrogen per day.

It occasionally happens, with cases of this kind, that there is no commensurate increase in the nonprotein nitrogen of the blood during a period of observation. This gives rise to the question: where is this retained nitrogen stored? The mere fact of nitrogen retention with normal individuals can be explained in only two ways—growth; and the building of new tissues, as, for example, during periods of convalescence from some diseases. With individuals who are obviously sick, either of these explanations is untenable and some third possibility must be entertained. Again, it was observed, when these cases of chronic nephritis were studied according to metabolic methods, that during periods of nitrogen loss when the output considerably exceeded the intake, there was not always a drop in the nonprotein nitrogen of the blood nearly sufficient to explain the minus balance. We have many records showing a nitrogen loss of 0.3 gm. daily, over a period of two weeks—a total loss of more than 5 gm., and during this period the nonprotein nitrogen might not change within the limits of error or might drop 0.020 gm. per 100 c.c. For a person weighing 75 kilos, this would be a total loss of about 1.5 gm., perhaps, hardly more. For these reasons it seemed necessary to make a more exhaustive examination of the tissues in order to determine what became of this retained nitrogen.

It will be understood readily that a large number of the cases were studied before we were able to secure data on tissue analyses, since some of the patients studied did not die in the hospital, and many who did die, could not be examined postmortem. However, at the

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\* From the Medical Clinic of the New York Hospital.

present time we have tissue analyses from fourteen cases of nephritis which evidenced nitrogen retention during life and the tissues were examined chemically after death.

The chemical examination of these tissues was conducted not without considerable technical difficulty. It was impossible, of course, to examine samples of all the tissues of the body. On account of mass, it seemed reasonable to suppose that the muscles were implicated largely in nitrogen retention, and for theoretical considerations, liver analyses are desirable. The disturbances of the central nervous system in late nephritis, indicates the desirability of analyses of the brain.

Autolysis probably begins antemortem; at least we know that in certain organs it progresses with astonishing rapidity, postmortem. For this reason tissues were analyzed only when the necropsy was done within six hours after death. Even with this precaution, we found that results of the brain analyses for nonprotein nitrogen were so fluctuating, and that the water content was so extremely variable, that no dependable fact could be deduced. Accordingly, all of these results are thrown out. We are also somewhat doubtful about our analyses of liver tissues, because of extreme variability in water content. The tissues have to be minced prior to extraction, and in the process of mincing, blood and water are expressed, and this is a confusing element in manipulation. It is hoped that in the future this investigation of liver tissue can be carried out by a definite technic which I will here suggest for the benefit of anyone who may be interested in this subject.

It is possible, by using methods familiar to bacteriologists, to desiccate tissues after freezing. This method is used for pulverizing bacteria, and it could be applied to the analysis of liver tissue without great difficulty, if the necessary equipment were available. The liver tissue so desiccated could be pulverized and extracted.

Muscle tissue from the psoas muscle was employed, because of its relative freedom from fat. No particular difficulties were encountered in making these analyses, and the results seem clear cut.

Considerable difficulty was experienced in establishing a normal for these tissue analyses. Obviously, all cases showing any nephritis at necropsy had to be excluded—a majority, even when there had been no reason during life to suspect impairment of renal function. The result of our analyses appears to indicate that the normal for extract nitrogen is always less than 1.00 gm. per 100 gm. of dry substance. Tissue from cases of pneumonia often exceeded this figure to a slight extent, but the kidneys from these cases usually show cloudy swelling, and the question is, are they functionally normal. These analyses are not included in the table, since the interpretation is dubious.

There is a notable variation in the water content of muscle and all tissues, and the variation is most marked when edema is a possibility. On this account a basis of comparison is secured by computing the extract nitrogen per grams of dry substance (last column of table), the only basis of comparison where several variables are involved.

## ANALYSIS OF PSOAS MUSCLE

Anatomic Diagnosis	Water, per Cent.	Total N <sub>2</sub> per Cent., Gm.	Extract N <sub>2</sub> per Cent., Gm.	Extract N <sub>2</sub> per Cent. of Dry Substance, Gm.
4. Sepsis.....	72.9	2.92	0.24	0.88
5. Peritonitis, acute .....	74.9	3.18	0.18	0.71
11. Fractured skull; cerebral hemorrhage..	74.8	3.16	0.22	0.87
9. Bronchopneumonia; postoperative ap- pendicitis .....	69.03	3.39	0.28	0.90
7. Cerebral embolism; cardiac.....	72.6	3.46	0.31	1.13
15. Acute nephritis (postscarlatinal).....	78.11	3.34	0.38	1.73
20. Parenchymatous nephritis .....	74.5	3.58	0.24	0.94
21. Parenchymatous nephritis .....	84.5	2.83	0.22	1.69
24. Parenchymatous nephritis, large white kidney .....	79.8	3.11	0.22	1.88
13. Chronic nephritis, granular kidney..	78.39	3.23	0.34	1.57
14. Chronic nephritis, granular kidney..	73.85	2.02	0.28	1.08
16. Chronic nephritis, contracted kidney	78.88	3.04	0.38	1.79
17. Hydronephrosis, chronic nephritis...	78.23	3.30	0.36	1.65
3. Cerebral hemorrhage, chronic ne- phritis .....	77.7	3.03	0.37	1.65
27. No kidney .....	78.4	....	0.38	1.75

The first four analyses are cases selected from the control series. For this series, we used only such cases as gave no evidence of renal disease during life and where, at necropsy, the kidneys were found to be relatively normal.

In Case 7 there was a slight increase of the nonprotein nitrogen during life. No metabolic study could be carried out. It is interesting that the nitrogen retention found with decompensated cardiac disease (to which I have called attention in an earlier paper) should be manifested also by an increase of extract nitrogen in the tissues.

Case 15 is the only example of nephritis following directly on scarlet fever that I have been able to study with proper care. Clinically, this case was of a mixed type, since there were disturbances of both salt and nitrogen metabolism. The slightly elevated water content of the muscle indicates a residual edema. The high figure for extract nitrogen corresponds with the clinical and laboratory findings during life.

Cases 20, 21 and 24 were diagnosed during life as parenchymatous nephritis. The functional disturbances concerned the water and salt excretion, and there was the usual normal or low blood concentration of extract nitrogen. A fact of considerable interest was noted in the metabolism studies of these cases. All showed a slight plus balance. In this respect they are quite like mild cases of interstitial nephritis.

In no case of what seemed to be parenchymatous nephritis that we have been able to study, has there been the minus balance or equilibrium expected. All showed some retention. This retention was always slight, but if the period of observation were ten days or more, it became evident—provided the nitrogen intake was 15 gm. This was a matter of considerable speculation, and was one of the reasons for this tissue study. Cases 21 and 24 seem to confirm the metabolic studies; case 20 does not.

This patient (Case 20) was studied about two weeks before death. At the time of the metabolism studies there was general anasarca—later a diuresis occurred and the edema vanished (with water content of muscle), following this the patient had a convulsive seizure which ended in death.

It has been accepted that there is no significant disturbance of the protein metabolism to be noted in cases of pure parenchymatous nephritis. The evidence on which this conception rests is open to some question. The water content of blood is variable; when there is edema observations of specific gravity, water content and dry substance all indicate an hydremic condition of the blood. The customary technic for estimating the nonprotein nitrogen of the blood takes no account of this. A volume of blood, from 25 to 50 c.c., is measured and the extract nitrogen determined in this volume. Comparison of an hydremic blood with normal blood thus introduces an obvious error which we have long recognized and discounted in blood counts and hemoglobin estimations. For correct facts as to the nonprotein nitrogen of blood, the specific gravity of the blood, or the water content must be known, and from these computations derived as to nitrogen.<sup>1</sup>

The cases of chronic interstitial nephritis show, with one exception, an increase of extract nitrogen of 50 per cent. or more above normal. All of these patients had been treated by means of low nitrogen diets, and all had shown a negative balance for variable periods. The tissue accumulation is the more significant on this account.

The last case (Case 27) is of interest. The sole functioning kidney was removed on account of uncontrollable hemorrhage following an operation for perinephritic abscess. At necropsy the remaining kidney was found to be a fetal remnant about one inch in length and without functioning elements.

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1. Some interesting computations may be made from data given in the paper of Butterfield (*Am. J. M. Sc.* **151**:63 (Jan.) 1916) dealing with the physical characteristics of blood from nephritic cases. With normals there is a specific gravity of 1.027, a dry residue of 9.8 per cent. and a protein content of 8.1 per cent.; when edema occurs with nephritis, then the specific gravity may fall to 1.015, the dry residue to 6.3 per cent. and the protein content to 4.3 per cent., nearly half the normal.

The data offered in this communication are neither complete nor conclusive. The evidence at hand simply supports an inference that has always been made, namely, that retained nitrogen cannot be retained exclusively in the blood. There seems also a possibility that disturbances of protein metabolism is a characteristic of nephritis generally, and that differences with types of nephritis are differences only of degree.

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## STUDIES ON EPINEPHRIN. I

EFFECTS OF THE INJECTION OF EPINEPHRIN IN SOLDIERS WITH  
"IRRITABLE HEART" \*

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With the mobilization of our troops, and especially the drafted troops, at the entrance of this country into the war, the problem of sorting the fit from the unfit was one of the first to come up. In attempting to solve this many other problems for the medical corps arose. Among these, one of the most interesting and at the same time one of the most baffling, was the problem of determining the etiologic factors of the symptom complex observed by DaCosta during the Civil war and described by him as the "irritable heart of soldiers." In the present war this condition has been termed by Lewis the "effort syndrome." As this problem has been studied more carefully, it has proved to be a many sided one, and it now seems quite certain that the symptom complex represents several clinical entities. Many opinions have been advanced as to the etiologic factors underlying this condition but few facts have been brought forward in their support. Thus hyperthyroidism has been held by some observers to be the chief factor, while many others regard it as at least a significant factor in the production of the symptom complex.

It was to determine the relation of the thyroid gland to this condition that a study of the basal metabolism in a number of these cases was begun at the U. S. Army General Hospital No. 9.<sup>1</sup> From this study it was concluded that hyperthyroidism did not play a significant rôle in the production of the symptom complex of "irritable heart of soldiers."

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\* This investigation was suggested by and started under the direction of Major Francis W. Peabody, M. C., U. S. Army, and completed under the direction of Capt. Bertnard Smith, M. C., U. S. Army, at U. S. Army General Hospital No. 9, Lakewood, N. J.

1. Peabody, Francis W., Wearn, Joseph T., and Tompkins, Edna H.: The Basal Metabolism in Cases of the "Irritable Heart of Soldiers," *Med. Clin. North Am.*, September, 1918.

In order to make the investigation of the question of the rôle of the thyroid gland more comprehensive, it was decided to employ at the same time the epinephrin test. Goetsch has reported<sup>2</sup> that cases of hyperthyroidism give a very marked reaction to small doses of this drug. It was thought that the observations on the basal metabolism would form an interesting check on the value of the epinephrin test. It was soon observed that some of the cases with a normal basal metabolism and with histories not typical of hyperthyroidism showed a definite hypersensitiveness to epinephrin. This group of soldiers exhibited certain signs and symptoms which made them resemble superficially cases of the so-called "forme fruste" of exophthalmic goiter, and, indeed, many of them were sent to this hospital with a transfer diagnosis of hyperthyroidism. In addition to this group there were many other cases of so-called "irritable heart" which reacted abnormally to epinephrin but did not show any signs of hyperthyroidism. Inasmuch as this excessive reaction to epinephrin suggested a hypersensitiveness of the sympathetic autonomic nervous system, it was determined to make a more careful study of these patients.

#### LITERATURE

The literature concerning the action of epinephrin in man has been reviewed by Goetsch.<sup>3</sup> Frazier and Wilson,<sup>4</sup> working in England, made observations on ten cases of "irritable heart" and four normal men, following the injection of 0.01 gm. of epinephrin intravenously. They concluded that the sympathetic nervous system was more susceptible to the action of epinephrin in cases of "irritable heart" than in normal men.

#### PHYSIOLOGIC ACTION OF EPINEPHRIN

The physiologic action of epinephrin has been worked out experimentally in animals and to some extent by injection in man, but despite the large amount of work done there still remain many details of its actions which are not clear. It seems to be generally accepted, however, that epinephrin has a selective action on the sympathetic autonomic nerve terminals. It is on this fact that the interpretation of this work is based.

#### TECHNIC

The technic followed is the same as that used by Goetsch in studying the hypersensitiveness to epinephrin of patients with exophthalmic goiter. The patients remain at absolute rest in bed for a period of

2. Goetsch, E.: *Newer Methods in the Diagnosis of Thyroid Disorders: Pathological and Clinical*, New York State J. M. **18**:259 (July) 1918.

3. Loc. cit.

4. Frazier, Francis, and Wilson, R. M.: *The Sympathetic Nervous System and the "Irritable Heart of Soldiers,"* Brit. M. J. **2**:27 (July 13) 1918.

one hour. If there is restlessness or apprehension they should be reassured, and every effort made to obtain mental, as well as physical quiet. At the end of the rest period control readings of the blood pressure, pulse and respiratory rates are made at five minute intervals. Also at this time a note is made as to the presence of nervousness, precordial pain, dizziness, palpitation, or any other symptoms which may be significant. Likewise the objective condition of the patient is observed, and it is recorded if any of the following signs are present: tremor of the hands, sweating, coldness of the hands, throbbing of the neck, epigastrium, or over the precordium, and pallor or flushing. At the end of an hour's rest in bed the patient is usually quiet and has few complaints; the blood pressure and heart rate are normal, or there may be a slight tachycardia (in sharp contrast to the patient with exophthalmic goiter in whom a more marked tachycardia persists even when at rest in bed). Likewise after the rest period there is little to record from an objective or subjective standpoint. If this condition approaching the normal has not been attained then the control readings should continue further, for with nervousness, tremor, sweating, tachycardia, or possibly other prominent signs already present it would be difficult to judge the effect of the epinephrin. In a few patients the control readings of blood pressure and pulse remained at a level slightly above the normal, but the injection of epinephrin was carried out after they became constant. In a number of patients venepuncture was done at the end of the rest period for blood sugar determinations, but when this or any other disturbing factor is introduced it is necessary that subsequent control readings be made, and these should agree with the preliminary readings before the test can proceed.

After satisfactory control readings have been made, 0.5 c.c. of a 1:1,000 solution of epinephrin, freshly prepared, is injected deep into the deltoid muscle. In all of these tests the solution was made by adding one  $\frac{3}{200}$  grain of Parke, Davis & Co. adrenalin brand of epinephrin tablet to 1 c.c. of water, thereby making a 1:1,000 solution.

After the injection four or five readings are made of the blood pressure, pulse and respiratory rates at two or three minute intervals, and also at these times any change in the objective or subjective condition of the patient is noted. After the first few observations, readings are continued at five minute intervals until one hour after the injection, when ten minute readings are made for a period of one-half hour, thus making the observation period one and one-half hours from the time of the injection. From our experience at Lakewood it would seem that the time of observation could safely be cut to one hour, as we have failed to observe anything of importance after that length of time.

## REACTION TO EPINEPHRIN

A typical positive reaction manifests itself on the average of about twelve minutes after the injection by a rise in systolic blood pressure, increased pulse rate and certain characteristic changes in the subjective and objective conditions of the patient. There may be restlessness, complaints of nervousness, precordial pain, palpitation, and frequently apprehension. Pallor or flushing may be present. A fine tremor is very characteristic, and while it usually only involves the hands it may become general and very marked, occasionally to the extent of shaking the bed. In a number of cases there was tremor of the eyelids. The hands usually become cold and often there is excessive sweating, especially in the palms. In some cases there was a definite dilatation of the pupils, while in others little change could be observed. Pulsation was frequently very marked in the neck and epigastrium and over the precordium. The patient often states that he experiences about the same symptoms that he had previously noted after exertion. The conditions just mentioned are very characteristic, and when they are present a hypersensitiveness to epinephrin is easily recognized without the aid of the blood pressure or pulse record.

The onset of the symptoms is usually simultaneous with the changes in blood pressure and pulse, and the symptoms vary in intensity with the changes in them. In a study of seventy-one charts of positive reactions in all types of "irritable heart" the average systolic blood pressure rise was found to be 24.5 mm. Twenty-five of these cases showed a rise of from 10 to 20 mm., twenty-six from 20 to 30 mm., sixteen from 30 to 40 mm., two from 40 to 50 mm., and in two cases the rise was over 50 mm., one being 52 mm. and the other 71 mm. The pulse pressure is increased in all of the positive cases, either the diastolic pressure remaining constant while the systolic pressure rises, or what is more characteristic, the diastolic pressure falling during the height of the reaction and returning to normal with the drop in systolic blood pressure.

In a study of the pulse curve in seventy-one positive cases the average increase in pulse rate was found to be 26 to the minute. Four cases showed an increase in pulse rate from 1 to 10, twenty-seven from 10 to 20, twenty-one from 20 to 30, thirteen from 30 to 40, six from 40 to 50, the greatest increase being 46. During the course of some of the positive reactions various pulse irregularities have been noticed. Among the conditions observed have been marked sinus arrhythmia, extrasystoles and dropped beats. These findings were confirmed by electrocardiograms. A careful electrocardiographic study has been made following the injection of epinephrin and will be reported in a separate paper by Lieut. Harry D. Clough.

Observation of the respiratory rate and depth of respirations has been of little value in interpreting the reaction. The rate may be increased or decreased. In a number of cases there was slowing with an increase in depth of respiration, while in a few cases there was an increase to the remarkable rate of forty or fifty with very shallow breathing. In a study of the gaseous metabolism following the administration of epinephrin, which is reported in a separate paper,<sup>5</sup> the minute volume of air breathed was found to be increased in each case. In these same patients pneumographic tracings showed either an increased respiratory rate or an increase in the depth of respiration.

The onset of the reaction occurs about twelve minutes after the injection; the height is reached on the average in thirty-two minutes and the reaction is finished in approximately one hour. The effect of the epinephrin is transitory and the symptoms experienced are rarely worse than those induced in the patient by exercise.

Usually the reaction is clean-cut and no difficulty is experienced in its classification as it is either clearly positive or negative. There is, however, a small group of cases in which the reaction is less definite and the correct interpretation can be made only after a careful study of the entire clinical picture. Finally, there remains a still smaller number of cases which it is impossible to classify as either negative or positive, and this type of reaction has necessarily been designated as doubtful. In such cases the test has usually been repeated, but the second test has always been a repetition of the first. As an aid to the interpretation of the reaction the observations made during the test may conveniently be divided into three parts as follows:

1. Symptoms (precordial pain, nervousness, palpitation, etc.), and certain objective conditions as throbbing, pallor, flushing, cold extremities, tremor and sweating.

2. Blood pressure.

3. Pulse rate.

In a large number of cases changes in all three were present and the reaction was easily determined. In a very few cases there were fairly marked changes in blood pressure and pulse rate without subjective symptoms. In each case with subjective changes of importance, however, there was a corresponding change in pulse and blood pressure.

In an endeavor to interpret correctly the more or less doubtful cases, a study of the positive and negative reactions was made, and the following rule formulated: A positive reaction is characterized by

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5. Tompkins, Edna H.; Sturgis, Cyrus C., and Wearn, Joseph T.: *The Effects of Epinephrin Upon the Basal Metabolism in Soldiers with "Irritable Heart," in Hyperthyroidism and in Normal Men*, Arch. Int. Med., this issue, p. 269.

a rise in blood pressure of 10 mm. or more, associated with a rise in pulse rate of at least 10 to the minute, provided these are not isolated rises, and associated with the signs and symptoms such as tremor, pulsation, nervousness, precordial pain, dizziness or restlessness. It is impossible to make any statement that will definitely classify all cases, but the above, in our experience, has proved very satisfactory, except in those few cases with a fairly marked rise in blood pressure and pulse rate, without other changes. These have been regarded as positive reactions.

To meet the criticism that changes which might be interpreted as a positive reaction could result from the stimulus of an intramuscular injection in a nervous individual, several patients known to be sensitive to epinephrin were given the test according to the usual technic except that sterile water instead of epinephrin was given intramuscularly. There were no changes of importance in the hour and a half period following. At the end of this period, these patients were given the usual dose of 0.5 c.c. of a 1:1,000 solution of epinephrin, which produced a typical positive reaction with all of the classical signs. As further evidence that a painful stimulus will not produce changes indicating a positive reaction, it was noted that when venepuncture to secure blood for sugar determinations was done on ten epinephrin sensitive cases immediately before the epinephrin was injected it did not cause any change in the blood pressure, pulse or objective or subjective conditions of the patient. In a few cases a slight change has resulted in the blood pressure and pulse rate immediately following the epinephrin injection, but this was probably psychic. This change is easily distinguished from the effect of the epinephrin by its early occurrence, while the epinephrin effect usually appears about twelve minutes after the injection. Furthermore, the change is transitory, rarely persisting more than one observation while the true epinephrin effect is in the form of a curve.

#### OBSERVATIONS ON NORMAL SOLDIERS

In order to control the epinephrin test properly, it was necessary to determine the effect of 0.5 c.c. of a 1:1,000 solution of epinephrin in normal men. To do this, permission was obtained from the division surgeon and commanding officer of the 109th Sanitary Train, then stationed at Camp Dix, to try the test on twenty-six men of that organization who volunteered for that purpose. These men were not picked men, but all who offered themselves were accepted; they had, however, been through fourteen months of military training and were in excellent physical condition. In not a single case was there a positive reaction to epinephrin as judged by the rule formulated to deter-

mine a positive or negative case. The blood pressure and pulse curves showed slight, if any, change, and the characteristic subjective and objective conditions of the epinephrin sensitive group were lacking. In distinct contrast to the epinephrin sensitive patients with their marked restlessness and anxiety, the controls remained perfectly quiet, some of the men reading throughout the greater part of the test, while others actually slept.

In a detailed study of the records of the twenty-six men the following facts were determined:

1. *Systolic Blood Pressure.*—There was a rise in the systolic blood pressure in twenty-one of the twenty-six cases, the rise being small, usually between 6 and 12 mm. In five cases, the rise was over 12 mm., and in one case it reached 18 mm. The average rise for the twenty-six cases was 7 mm.

2. *Pulse Pressure.*—In fourteen of the twenty-six cases there was a measurable increase (over 5 mm.) in the pulse pressure. The increase was usually between 10 and 12 mm.; there were two cases with an increase over 12 mm., both being 18 mm.

3. *Pulse Rate.*—Of the twenty-six cases, sixteen showed an increase in pulse rate of over five beats to the minute. The average of the pulse rate increase was six for all of the cases.

4. *Respirations.*—Here it is difficult to draw conclusions, as twenty-one of the twenty-six cases showed an increase of from one to eight to the minute, but in nine cases there also was a drop. In two cases there was a drop and in two cases no change.

5. *Symptoms and Signs.*—There was slight pulsation in sixteen of the twenty-six cases, ten showed slight tremor of the hands, seven flushing, and three transitory pallor. In only two cases were there subjective symptoms, one man complaining of slight nervousness and the other of weakness. In all of the cases the pulsation, tremor, pallor and flushing were of a minor degree and of very short duration. Hence, it is seen that while the normal man may show slight changes following the injection of a small dose of epinephrin, all of the changes are of such a minor degree that they could not possibly be confused with an epinephrin positive reaction. They are never in the combination or of the intensity seen in epinephrin sensitive individuals.

#### CLINICAL STUDIES

A large proportion of the patients with "irritable heart" in General Hospital No. 9 were sent to the hospital from camps in the United States where they had developed symptoms of the "effort syndrome" early in their military career. As will be seen, the symptoms existed

TABLE 1.—CLINICAL CHART OF—

No.	Name	Hospital Number	Age	Race	Military Service	Active Duty	Symptoms Causing Patient to Fall Out	Occupation	Character of	Time Lost From Work
1	M. C. H.	2677	30	U. S.	5½ months	1 day	Fainted	Clerk (book-keeper)	Light	3 to 4 days a month in past year
2	B. S.	1103	20	U. S.	12 months	6 months	Palpitation, precordial pain	Dairy worker	Light	None
3	J. J. H.	766	23	U. S.	14 months	1 month	Dyspnea and precordial pain	Mechanical engineer	Light	None
4	A. M.	875	23	U. S.	3½ months	1 week	Fainted	Cook	Light	No work for 2½ years
5	W. C. S.	1149	25	U. S.	4 months	3 days	Precordial pain, dyspnea and dizziness	Railroad hostler	Light	About 1 month in 7
6	G. W. C.	1354	25	U. S.	10 months	1 week	Dizziness, dyspnea, palpitation	Student	Light	None
7	L. F. B.	2860	24	U. S.	5½ months	1 week	Dyspnea, palpitation, fainted	Barber	Light	2 days a week for past 2 years
8	E. M. H.	775	23	U. S.	19 months	12 months	Precordial pain, dyspnea	Milkman	Light	None
9	S. H. G.	1284	26	U. S.	7 months	2 days	Weakness, dizziness	Assistant cashier	Light	About 10 days a year
10	E. M.	2487	24	U. S.	6 months	3 weeks	Palpitation, dyspnea, weakness	Drug clerk	Light	About 1 month a year
11	O. R. S.	2569	19	U. S.	14 months	4 months	Precordial pain	Auto mechanics helper	Very light	About 3 weeks a year
12	A. M.	926	24	Russian Jew	5½ months	2 weeks	Precordial pain, dyspnea, weakness	Tailor	Light	Worked less than half time for past 3 years
13	G. S.	1110	23	U. S.	16 months	2 weeks	Dizzy, precordial pain, dyspnea, weakness	Shoemaker	Very light	3 or 4 days a month for past 5 years
14	F. K.	819	26	U. S.	10 months	6 months	Fainted	Printer	*	*
15	A. W.	1144	28	U. S.	3½ months	None	Pain in side	Hopper filler	Light	1 week a month for past 4 years
16	R. D.	1185	23	U. S.	3½ months	3 weeks	Weakness, precordial pain	Printer	Light	1 day in 2 months
17	G. A.	729	24	U. S.	10 months	2 weeks	Pain in back and feet, dyspnea	Sailor	Light	Stopped at work frequently
18	J. F. F.	423	23	U. S.	12 months	2 months	Dyspnea	Freight checker	Light	1 day a week
19	C. R. B.	723	23	U. S.	12 months	6 months light duty	Precordial pain	Shoe worker	Light	2 to 3 days a month
20	J. C. F.	2587	26	U. S.	18 months	7 months	Dyspnea, precordial pain, dizziness	Manager retail grocery	Moderate	None
21	G. S.	929	29	Austria	6 months	None	Precordial pain	Weaver	Light	1 week in 3
22	D. R.	1109	22	U. S.	13 months	2 weeks	Dyspnea, pain in the legs	Waiter	Light	Frequently lost time
23	C. H.	405	28	U. S.	5 months	2 days	Precordial pain, dizziness	Drove garbage wagon	Light	About 3 days a week
24	G. H.	1227	31	U. S.	6 months	2 weeks	Dizziness and pain in stomach	Furniture repairer	Light	Lost much time
25	I. G. Z.	1230	23	U. S.	4 months	5 weeks	Dizzy spells and headache	Farmer	Very light	Occasionally
26	C. H. H.	949	24	U. S.	12 months	3 weeks	Dyspnea, weakness	Railroad clerk	Light	2 to 5 days a month
27	W. H. P.	2580	30	U. S.	18 months	9 months light duty	Precordial pain abdominal pain	Hat maker	Light	Several days a month
28	E. I. K.	1226	23	U. S.	4½ months	2 weeks	Weak spells "heart rapid"	None for 4 years	.....	.....
29	W. D. B.	1167	23	U. S.	4 months	12 days	Dizziness and nausea	Farmer	Light	Frequently lost time
30	D. C.	1148	26	Irish	3 months	2 weeks	Dyspnea and exhaustion	Chauffeur	Light	Worked 2 hours daily
31	J. K.	1177	31	U. S.	12 months	6 weeks	Precordial pain, nervousness	Shipping clerk	Light	2 to 3 days a month
32	H. R.	1251	24	U. S.	5 months	9 days	Palpitation, precordial pain	Machinist	Light	Lost weeks at a time

—EPINEPHRIN POSITIVE PATIENTS

Exercise	Education	Special Points of History	Duration of Symptoms	Alleged Etiology	Weakness	Dizziness	Blurred Vision	Fainting	Excitability	Nervousness	Dyspnea	Preordial Pain	Special Symptoms	Remarks
None	3 years high school, bus. coll. 10 mo.	Always frail	5 years	"Worry"	+	+	0	+	+	+	+	+	Palpitation	Sleek a great deal as child, never strong
Baseball but always short of wind	4th grade at 14 years	Good health strong	7 months	"Mumps"	0	+	+	0	+	+	+	+	Palpitation	
Always athletic	3 years high school	Good health	9 months	"Heavy cold"	+	+	+	0	+	+	+	+	Palpitation	
None as a rule	5th grade at 14 years	Left testicle removed 1916	3 years	None	+	+	+	+	+	+	0	+	Abd. and pain in back	
Baseball a little, none for 3 years	6th grade at 14 years	Never strong	11 years	"Injury to head"	+	+	+	0	+	+	+	+	.....	Healthy until 11 years ago
None	3 years law school	Always had to be careful	18 years	"Pneumonia at 7 years"	+	+	+	+	+	+	+	+	Palpitation	
None for 2 years	Finished high school at 18 years	Always frail	2½ years	"Heavy work"	0	+	+	+	+	+	+	+	Palpitation	Asthma since childhood
Always athletic	6th grade at 14 years	Always strong	7 months	"Worked too hard"	0	+	+	+	+	+	+	+	.....	
Light exercise	Finished high school	Knew he was not equal to the work	8 months	"Overwork"	+	+	+	+	+	+	+	+	.....	Walked 21 miles in a day, 1 yr. ago
None	8th grade at 17 years	.....	4½ years	None	+	0	+	0	+	+	+	+	"Fast heart"	
None	8th grade at 16 years	Always sickly	16 years	"Sick when a baby"	+	+	+	+	+	+	+	+	.....	
None	None	Never able to work hard	4 years	None	+	+	+	0	+	+	+	+	Palpitation	
Very light rarely	8th grade	Always weak and nervous	4 years	"Inside work"	+	+	+	0	+	+	+	+	.....	
None	4th grade at 11 years	Always weak, doctored 7 years	4 months All his life	"Working in hot room"	+	+	+	+	+	+	+	+	.....	Always weak
Breathing exercises	2 years high school	Always favored	Lifetime	None	+	+	+	+	+	+	+	+	.....	Weakness main symptom
None	2d grade at 16 years	.....	5 years	"Typhoid"	+	+	+	+	+	+	+	+	.....	Short of wind from feeling in throat
None	2 years high school	.....	Lifetime	"Born with it"	+	+	+	0	+	+	+	+	.....	Always weak and nervous
Very little	2 years high school	.....	6 years	None	+	+	+	+	+	+	+	+	.....	Pain left chest and shoulder
None	8th grade	Always healthy	1 year	None	+	+	+	+	0	0	+	+	Swelling of hands and feet	
None	9 years in Austria	"Coughed and spit blood"	4 years	"Cough and malaria"	+	+	+	+	+	+	+	+	Irritable	
None	5th grade at 14 years	.....	Lifetime	"Inherited"	+	+	+	+	+	+	+	+	Always nervous and weak	
None	3 or 4 years in school	.....	Lifetime	"Inherited"	+	+	+	+	+	+	+	+	Weak legs	
Walked 1 mile daily	2d grade	.....	Lifetime	None	+	+	+	0	+	+	+	+	.....	Flat feet
Walked 3 miles daily	Finished high school	.....	Lifetime	"Mother had TB when he was born"	+	+	+	0	+	+	+	+	.....	
None	1 year college	.....	Since entering army	"Army work"	+	+	+	+	+	+	+	+	Swelling in the neck	
Could not stand it	8th grade	.....	Lifetime	None	+	+	+	0	+	+	+	+	.....	
None	4th grade at 14 years	.....	7 years	"Nocturnal emissions"	+	+	+	0	+	+	+	+	.....	
None	3d grade	Chorea in childhood	Lifetime	"Meningitis when baby"	+	+	+	+	+	+	+	+	Convulsions?	
None	6th grade	.....	8 years	None	+	+	+	+	+	+	+	+	.....	
None	8th grade	.....	Lifetime	None	+	+	+	0	+	+	+	+	.....	
None	2 years high school	.....	Lifetime	"Croup when baby"	+	+	+	0	+	+	+	+	.....	Stomach trouble

TABLE 2.—CLINICAL CHART OF—

No.	Name	Hospital Number	Age	Race	Military Service	Active Duty	Symptoms Causing Patient to Fall Out	Occupation	Character of	Time Lost From Work
1	R. E.	1258	23	U. S.	3 months	1 week	Dizziness, weakness, precordial pain	Bell boy, chauffeur	Very light	About 2 months a year
2	F. A. O.	1285	24	U. S.	12 months	1 week	Weakness, precordial pain, blurred vision	Farmer	Moderate	1 to 2 months a year
3	W. P.	932	23	Italy	13 months	8 weeks	Precordial pain, dizziness, weakness	Teamster	Light	Day or two a month
4	F. P.	1067	29	Italy	4 months	1 week	Weakness, pain in back and legs	Fruit store	Light	About 1 week a month for years
5	G. W.	1423	22	U. S.	4½ months	1 month	Dyspnea and precordial pain	Farmer, coal miner	Heavy	Month out of each year
6	E. J. G.	1069	24	U. S.	4 months	3 weeks	Dyspnea and weakness	Clerk	Light	Very little
7	F. K.	711	25	Austrian Jew	4 months	5 days	Weakness, dizziness, nervousness	Furrier	Very light	4 or 5 months a year
8	W. Z.	873	25	U. S.	4 months	6 days	Fainted	Barber	Light	Worked 2 days a week
9	R. C.	874	24	U. S.	4½ months	1 week	Flat feet	Painter, travelling salesman	Light	2 to 3 days a week
10	G. D.	868	23	U. S.	3½ months	3 weeks	Dizziness	Department store clerk	Light	No work for 18 months
11	N. G.	1100	22	U. S.	17 months	11 months light duty	Dizziness	Salesman	Light	None
12	N. L.	1542	19	U. S.	14 months	2 days	Dyspnea and dizziness	Barber	Light	2 to 3 days a week
13	W. W.	1259	24	U. S.	3 months	3 weeks	Shortwinded, nervousness	Auto mechanic	Light	1 day in 2 weeks
14	T. P.	1228	22	U. S.	3 months	15 days	Dizziness and precordial pain	Drug clerk	Light	Practically none

prior to entrance into the army and were merely accentuated by the nervous and physical strain in the camps. This type of individual is frequently seen in civil life, where he is often classed as neurasthenic, and cannot be regarded strictly as a product of the war. They represent the group of patients with "irritable heart" whose symptoms have existed for a long time as contrasted to the cases whose symptoms are of short duration and date from some acute infection or nervous or physical strain. It is to the former group of patients particularly that attention is directed in the present paper. Incidental reference will be made to the epinephrin reaction in patients with "irritable heart" whose symptoms date from severe nervous or physical strain or from acute infections. No cases following "gassing" have been studied.

Those falling into the group with symptoms of long duration frequently date these symptoms back to childhood, and many state that they "inherited" them. In fact, it is the exceptional case in which the symptoms do not date back a number of years. They are usually the

## —EPINEPHRIN NEGATIVE PATIENTS

Exercise	Education	Special Points of History	Duration of Symptoms	Alleged Etiology	Weakness	Dizziness	Blurred Vision	Fainting	Excitability	Nervousness	Dyspnea	Precordial Pain	Special Symptoms	Remarks
Active until 14 years	5th grade at 14 years	Always nervous	9 years	None	+	+	+	+	+	+	+	+		
Baseball but always dyspneic	5th grade at 16 years	Always weak	12 years	None	+	+	+	0	+	+	+	+	.....	"Knew he could not stand it when he joined"
Never because "short winded"	School 3 months	"Doctored a good deal"	Lifetime	None	+	+	+	0	+	+	+	+	.....	"Never felt good in his life"
None	None	Well until 10 years of age	19 years	Unknown illness	+	+	+	+	+	+	+	+		
Active until 4 years ago	8th grade at 14 years	.....	2 years	None	+	+	+	+	+	+	+	0		
None	18 months high school	Easily tired	Lifetime	None	+	+	+	0	+	+	+	+	Palpitation at 14 yrs.	"Headaches and indigestion"
None	None	Always weak	Lifetime	None	+	+	+	+	+	+	+	+		
Walked half mile daily	6th grade at 18 years	.....	Lifetime	None	+	+	+	+	+	+	+	+	Incontinent at times	"Always weak and had dyspnea"
Athletic	3 years high school	.....	10 years	"Stomach trouble"	+	+	0	+	+	+	+	+	Palpitation	"Never strong since 14 yrs."
None	1 year high school	Always weak	Lifetime	"Born with it"	+	+	+	0	+	+	+	0	Throat trouble	
Athletic	Through high school	Always healthy	7 months	"Overwork"	+	+	+	0	0	+	+	+	Irritable	
None	5th grade	Always sickly	Lifetime	"Inherited"	+	+	+	+	+	+	+	+		
None	None	.....	Lifetime	"Inherited"	+	+	0	+	+	+	+	+	Always nervous	
None	8th grade	.....	Lifetime	None	+	+	+	+	+	+	+	+	.....	"Stomach trouble"

"delicate child"; they have been told in early life by the doctor that they had "heart trouble" and therefore must avoid any strain and all heavy work. As a result they have had to "favor" themselves. They were not allowed to play any of the more vigorous games, and if by chance they did try them, they had to give them up, for they soon found they could not keep pace with the other children. They got "short of breath"; they had "pain over the heart"; they felt weak and got tired. In school most of them had difficulties, as is shown in Tables 1 and 2, but this does not hold true for all of this group, for in exceptional cases they reached college.

As they grow older and the question of earning a livelihood confronts them they usually try several jobs or occupations, each successively lighter than the preceding one, until by the process of elimination they at last find one which can be adapted to themselves, and in which the work is so light that there is no strain and therefore their symptoms are less prominent. Nevertheless, their symptoms are easily

produced by exertion or nervous strain. Since their tendency is to "give in" easily to any discomfort, and to regard themselves as invalids it is quite characteristic for them to lose a considerable amount of time from their work. As a result of this their economic level is usually a low one. Such is their earlier life.

When called into the military service by the draft, or in a few cases by enlisting, they are brought face to face with a totally different existence. There is a considerable amount of physical exertion, and there is an element of nervous strain in it that to them looms very large. To succeed they must adapt themselves to these new conditions of life, for they can no longer adapt the conditions of life to their own personal limitations. They are started in light drill and immediately their symptoms begin to develop. As the severity of the drill is increased they begin to fall out, and when the hikes begin the active military careers of most of them come to an end. They fall out on account of "weakness," "dizziness," "pain over the heart," "shortness of breath," "palpitation," "blurring before the eyes," and quite often they faint. While many of the presenting symptoms suggest cardiac weakness, it is very striking that the most important underlying feature is often the tendency to general muscular fatigue. They complain of "being tired," and they give up to this feeling immediately. From Tables 1 and 2 it is interesting to note that when they arrive at the hospital, their actual military service may be measured in months, while their active duty is practically always measured in days or weeks. After the first few weeks their time is generally spent in the infirmaries or hospitals. The length of active duty of some of the cases in the tables deserves explanation. In Table 1, Cases 2, 8, 14, 19, 20 and 27, and in Table 2, Case 11, all did several months of active duty. In each of these cases active duty consisted of a few hours of light drill daily, and they were excused from all heavy drill and hikes. The active duty of Case 11 in Table 1, consisted of doing the work of a carpenter's assistant which he stated was very light work. The active duty of Case 19, Table 1, consisted of very light drill two or three times a week.

It will be noted in the tables that practically all of these men consider themselves "nervous" and easily excitable. A very striking fact was brought out on questioning them as to their reaction to gunfire. Twenty-eight of these men were questioned concerning their experiences on the rifle range. Eighteen patients stated that on going to the range during practice they began to tremble and "shake all over." The trembling often increased to such an extent that they had to give up practice. In two other instances officers noticed them shaking and sent them off the range. One fainted from excitement and had to be

sent to the hospital, and another collapsed and had to be carried from the range. Thus out of the twenty-eight questioned twenty-two, or 78.5 per cent. admitted that they could not stand gunfire. Two of the remaining six stated that they had never been within the sound of gunfire, and the other four stated that gunfire did not disturb them. Several admitted that they were afraid, while one stated that he was "scared to death." Others denied fear. The reaction to gunfire was about the same in the patients in Tables 1 and 2.

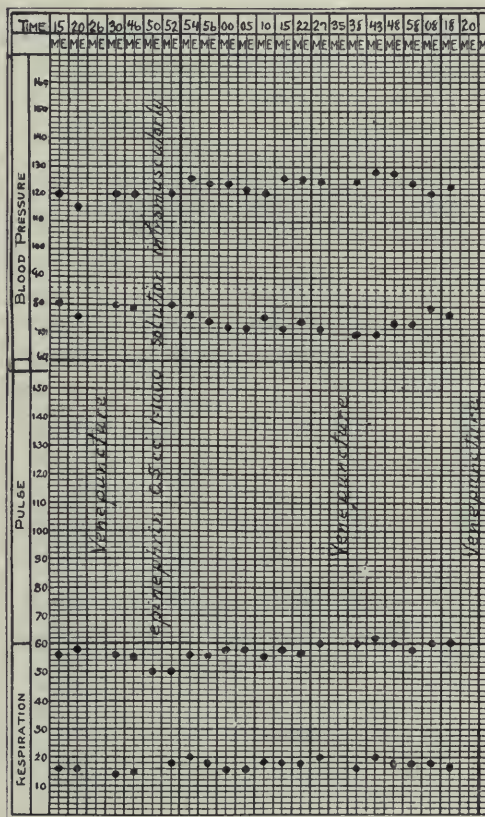


Chart 1.—Negative epinephrin reaction in a patient (F. B.) with mitral insufficiency. Venepuncture done twice during the observation period did not produce changes in the blood pressure, pulse or respiration.

Nervous hyperexcitability is also well illustrated in another way, and that is during the physical examination of the patients. When these men are examined by the ward surgeon the pulse rate is usually high, varying from 100 to 150 per minute. They may become flushed; they generally show a marked tremor of the hands and sometimes of both arms and legs; and they show increased sweating, most commonly

in the axilla and in the palms of the hands. They are quite apprehensive and the least noise startles them. If, however, they are allowed to lie quietly on the bed for an hour, all signs usually disappear. The pulse rate drops to normal, the tremor and sweating cease and they appear perfectly quiet. There are a few exceptions where a slight tremor or slightly increased pulse rate may persist. These

TABLE 3.—VERY SLIGHT TREMOR, PULSATION, QUESTIONABLE SWEATING, AND SLIGHT CHANGES IN THE TEMPERATURE OF THE HANDS PRESENT, BUT NOT ENOUGH TO INDICATE A POSITIVE REACTION

Time	Tremor	Sweating	Pulsations	Hands	Miscellaneous
9:10	Very slight	None	Very slight	Warm	Quiet; no flushing or pallor
9:20	Very slight	None	Very slight in neck	Warm	Quiet; no flushing or pallor
9:26 Venepuncture					
9:30	Very slight	Very slight	Very slight in neck	Warm	Quiet; no flushing or pallor
9:46	Very slight	Very slight	Very slight in neck	Warm	Quiet; no flushing or pallor
9:50 Epinephrin 0.5 c.c. 1:1,000 solution intramuscularly					
9:52	+	Very slight	+	Warm	Quiet; no flushing or pallor
9:54	+	Very slight	+	Warm	Quiet; no flushing or pallor
9:56	+	±	±	Warm	Quiet; no flushing or pallor
10:00	+	±	±	Fingers sl. cool	Quiet; no flushing or pallor
10:05	±	±	+	Fingers sl. cool	Quiet; no flushing or pallor
10:10	+	±	+	Fingers sl. cool	Quiet; no flushing or pallor
10:15	+	±	+	Fingers sl. cool	Quiet; no flushing or pallor
10:22	±	±	+	Fingers warm	Quiet; no flushing or pallor
10:27	±	±	+	Fingers warm	Quiet; no flushing or pallor
10:35 Venepuncture					
10:38	±	None	+	Fingers warm	Quiet; no flushing or pallor
10:43	+	None	±	Fingers warm	Quiet; no flushing or pallor
10:48	+	None	±	Fingers warm	Quiet; no flushing or pallor
10:58	±	None	±	Fingers warm	Quiet; no flushing or pallor
11:08	±	None	±	Fingers warm	Quiet; no flushing or pallor
11:18	±	None	±	Fingers warm	Quiet; no flushing or pallor
11:20 Venepuncture					

cases are in marked contrast to cases of hyperthyroidism whose pulse rate, tremor, etc., show only a slight decrease after an hour's rest. The physical examination of the heart usually shows a tachycardia, but otherwise nothing abnormal is made out.

We have injected epinephrin intramuscularly and made observations on seventy-three cases of the group of soldiers with "irritable heart" whose symptoms were of long standing. Of this number, forty-three, or 59 per cent., showed a definite hypersensitiveness to epinephrin

or gave a positive reaction as described above. Twenty-seven, or 37 per cent., showed no reaction. Three cases, or 4 per cent., gave a doubtful reaction.

The question naturally arises as to the difference between the cases showing positive and those showing negative reactions. After a careful clinical study of these two groups as charted in Tables 1 and 2 we have been unable thus far to find any differences, except that the reaction was more constant in those with pronounced neurotic tendencies.



Chart 2.—Record of patient (A. W.) showing characteristic changes of a positive reaction following repeated doses at an interval of one hour.

As stated above, no claim is made that this whole group represents any single clinical entity, and it seems possible, though we have no proof to offer, that the positive and negative groups may have a different etiology for their symptoms.

This reaction to epinephrin is not peculiar to the group whose symptoms have existed for a considerable length of time. Observations have been made on eighteen cases of "irritable heart" in which the

TABLE 4.—INJECTION OF 0.5 C.C. OF EPINEPHRIN REPEATED AT THE END OF AN HOUR IN PATIENT WITH "IRRITABLE HEART" WHOSE SYMPTOMS ARE OF LONG DURATION \*

Time	Tremor	Sweating	Flushing	Pulsations	Hands	Miscellaneous
12:05	+	0	+	Slight neck	Warm	Quiet
1:30	+	0	+	Slight neck	Warm	Quiet
1:56	+	+ palms	+	Neck, abdomen slight	Warm	Quiet
1:58 Epinephrin 0.5 c.c. of 1:1,000 solution intra- muscularly						
2:00	++	+	Pale	Neck, abdomen	Cold	Pain over heart, breathing deep
2:03	++	+	More color	Neck, abdomen	Cold	Not such deep breathing
2:08	++	+	+	+	Warmer	Definite precordial pain, quiet
2:15	++	++	++	++	Cold	Coughing, pain, heart fast
2:26	+++	++	++	+++	Cold	Pain in precordium
2:34	+++	+	++	+++	Cold	Pain in precordium, quleter
2:52	++	+	+	++	Cold	Occasional pain, quleter
2:58	+	0	+	+	Cold	Quiet
3:08	Very slight	+	+	+	Less cold	Quiet
3:20	Very slight	+	+	+	Same	Quiet
3:35	Very slight	+	+	+ Slight neck	Warm	Quiet, reaction over
4:05	Very	+	+	+	Warm	Occasional extra systole
4:14 Epinephrin 0.5 c.c. of 1:1,000 solution intra- muscularly						
4:17	+	+	+	+	Warm	Quiet, occasional extra systole
4:23	+	+	+	+	Warm	Quiet
4:28	+	+	+	+	Cooler	Restless
4:35	+	+	+	++	Cooler	Respiration very deep, restless
4:40	++	+	++	++	Cold	Respiration not so deep, restless
4:48	++	0	++	++	Cold	
4:45	++	0	++	++	Cold	Respiration not so deep, restless
5:00	+	0	++	++	Cold	Quiet
5:05	+	0	++	++	Cold	Quiet
5:10	+	0	++	++	Cold	Quiet
5:15	+	0	++	++	Cold	Quiet

\* Following each injection there was the typical reaction of a hypersensitive individual, the second being somewhat less marked than the first.

symptoms dated to some recent infection, such as rheumatic fever or pneumonia, previous to which they had been able to do full duty. Of these, six gave positive reactions to epinephrin and twelve gave no reaction. Observations were also made on a group of cases in which symptoms developed following some nervous or physical strain. Of seven of this type, five gave a positive reaction and two gave no reaction. The proportion of positive reactions in cases of "irritable heart" is in distinct contrast to the complete absence of positive reactions among normal trained soldiers.

In our experience the epinephrin reaction, when present, remains remarkably constant in individuals with symptoms of "effort syndrome" of long standing. It would seem that when such an individual once shows a positive reaction he retains his hypersensitiveness for a considerable length of time.

To determine if the reaction varied in a given patient at different periods, the tests were repeated in thirty cases at intervals of time

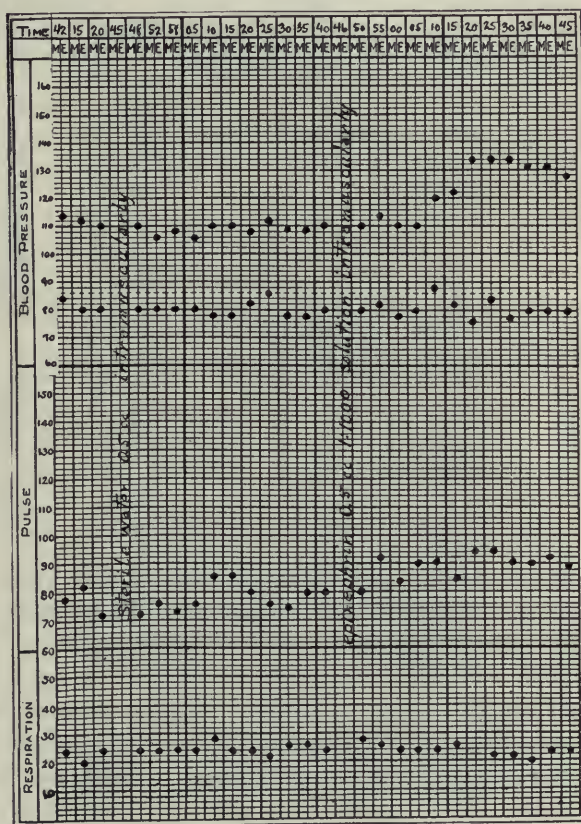


Chart 3.—Control test (A. M.) with the injection of 0.5 c.c. of sterile water intramuscularly without resultant change in the blood pressure, pulse or respiration. Observations were continued for one hour when 0.5 c.c. of a 1:1,000 solution of epinephrin was injected which produced a typical reaction.

varying between four and seventy-five days, the average being thirty days. Of nineteen cases which had previously given positive reactions, eighteen remained positive, while one case gave a doubtful reaction. In eleven epinephrin negative cases the reaction remained negative in nine, while in one it became positive and in another doubtful. In the case where the reaction changed from negative to positive the second reaction was obtained a few days after a tonsillectomy following which

the patient had complained of nervousness and possibly the operation could account for the increased sensitiveness. In a number of cases which gave reactions, the tests were repeated after the men had advanced several grades in the cardiac exercise classes, but this did not seem to affect the hypersensitiveness to epinephrin as the reaction remained positive.

TABLE 5.—NO CHANGE AFTER INJECTION OF 0.5 C.C. OF STERILE WATER. ONE HOUR LATER IN THE SAME PATIENT 0.5 C.C. OF 1:1,000 SOLUTION OF EPINEPHRIN PRODUCED THE CHARACTERISTIC PICTURE OF A POSITIVE REACTION WITH TREMOR, FLUSHING, PULSATION AND PALPITATION

Time	Tremor	Sweating	Flushing	Pulsations	Miscellaneous
2:20	+	0	0	0	Quiet
2:30	Suggestive	0	0	+	Quiet
2:45 H <sub>2</sub> O 0.5 c.c. intramuscularly					
2:48	+	0	0	+	Quiet
2:52	0	0	0	+	Quiet
2:58	0	0	0	+	Quiet
3:05	+	0	0	+	Quiet
3:20	0	0	0	+	Quiet
3:40	+	0	0	+	Quiet
3:46 Epinephrin 0.5 c.c. of 1:1,000 solu- tion intramuscularly					
3:55	+	0	0	+	Quiet
4:05	++	0	0	+	Quiet
4:15	++	0	0	++	Quiet
4:25	++	0	+	Head, neck, +++ abd.	"Heart thumping away"
4:35	++	0	+	+++	
4:40	++	0	+	++	Not so much throbbing
4:45	++	0	+	+	Quiet

On entrance to this hospital all of the patients had routine strength tests as done on the cardiovascular service.<sup>6</sup> The strength to weight ratio of the epinephrin positive patients was 17.4; that of the epinephrin negative patients was 16.8. Thus, there is practically no difference in the muscular strength of the two groups. Though some of the patients showed a measurable increase in strength, in general, they were not the type that progressed well in the exercises. Indeed, not one of the epinephrin negative men returned to full duty, and it will be seen from the table that the disposition of the positive and negative groups was about the same.

DISPOSITION OF SEVENTY-ONE CASES OF "IRRITABLE HEART"  
WITH SYMPTOMS OF LONG STANDING

Disposition	Epinephrin Positive		Epinephrin Negative	
	Number	Per cent.	Number	Per cent.
Domestic service .....	16	36.3	9	33.3
Cert. of disability.....	28	63.7	15	55.6
Full duty .....			3	11.

6. Smith, Bertnard: The Possibilities of Physical Development in Cases of Effort Syndrome by Means of Graded Exercises. Arch. Int. Med., this issue, p. 321.

In order to determine if the cases which gave a negative reaction with a small dose of epinephrin would react positively to a larger amount, ten men who had previously been classified as negative were given 1 c.c. of a 1:1,000 solution of epinephrin intramuscularly. In five of these cases there were no changes of importance following the increased dose, but in the five remaining cases there was a slight increase in pulse rate and blood pressure rise, varying between 10 and

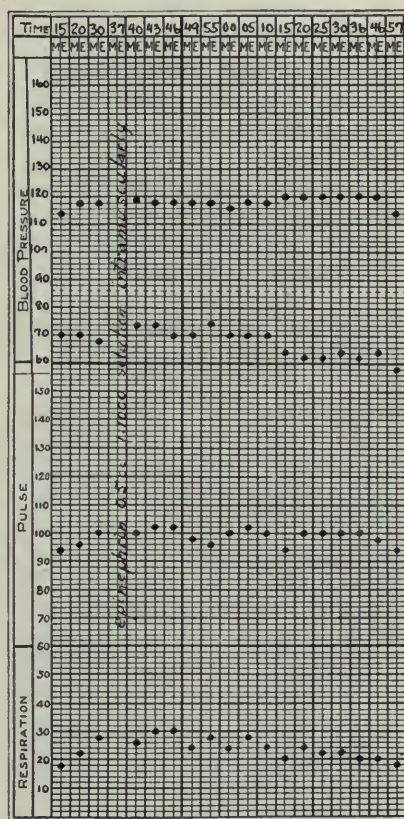


Chart 4.—Negative reaction in a patient (F. C.) with “irritable heart” whose symptoms date back for twelve years (Case 2 of the clinical chart of epinephrin negative patients). There is nothing to indicate even the slightest reaction to epinephrin.

20 mm. Also in some there was slight tremor and pulsation, but no restlessness or complaints of nervousness, precordial pain, etc. The picture was that of the reaction of a normal individual to a moderately large dose of epinephrin rather than that of a true hypersensitiveness to the drug. It would seem from these observations that the dose of 0.5 c.c. of a 1:1,000 solution of epinephrin is sufficient to produce all

the symptoms necessary to recognize a hypersensitiveness, while 1 c.c. of a 1:1,000 solution may produce moderate changes in a normal person.

## SUMMARY

The reaction to the intramuscular injection of a small dose (0.5 c.c. of a 1:1,000 solution) of epinephrin, has been studied in normal soldiers, and in a group of soldiers showing symptoms of so-called "irritable heart." Of twenty-six normal soldiers, who had gone through the grill of army training in its severest form for fourteen months, not one gave a positive reaction as judged by observation of pulse rate, blood pressure, objective signs or subjective symptoms.

TABLE 6.—SLIGHT CHANGES FOLLOWING THE INJECTION OF EPINEPHRIN, BUT NOT ENOUGH TO INDICATE A POSITIVE REACTION

Time	Tremor	Sweating	Flushing	Pulsations	Miscellaneous
2:15	.....	.....	.....	Slight neck	Quiet; no pulsation in fingers, not cold
2:25	Very slight	.....	.....	Slight neck	Quiet
2:30	Very slight	.....	.....	Slight neck	Quiet
2:37 Epinephrin 0.5 c.c. of 1:1,000 solution intramuscularly					
2:40	Very slight	.....	.....	Slight neck	Quiet
2:43	Very slight	.....	.....	Slight neck	Quiet
2:46	Very slight	.....	.....	Slight neck	Quiet
2:49	Very slight	.....	.....	Slight neck	Quiet
2:55	Very slight	.....	.....	Slight neck	Quiet
3:00	Very slight	.....	.....	Slight neck	Quiet
3:05	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:10	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:15	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:20	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:25	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:30	Slight increase	Slight	.....	Slight increase	Feels uneasy
3:35	Slight increase	Slight	.....	Slight neck	Slightly uneasy
3:46	Slight increase	Slight	.....	Slight neck	Slightly uneasy
3:56	Slight increase	Slight	.....	Slight neck	Slightly uneasy

Seventy-three patients with symptoms of "irritable heart" were studied. Their symptoms were of long duration and for the most part antedated their entrance into military life. Of this group about 60 per cent. gave a reaction which definitely indicated a hypersensitiveness to epinephrin. We know that epinephrin has a selective action on the sympathetic autonomic nervous system. One may, therefore, naturally suggest that the symptoms and signs induced in the positive cases are the result of a hypersensitive sympathetic autonomic nervous system. A careful clinical analysis, however, of the patients showing positive and negative reactions has revealed no essential clinical differences

between the two groups. One cannot state that the clinical condition of the patients who are sensitive to epinephrin depends in any way directly on the factors underlying the positive reaction. On the other hand, this is not at all impossible, and there is nothing to lead one to conclude that the factors causing the symptoms in the positive and negative groups are the same. It appears to be certain, however, that this group of patients is not good material from which to make a soldier.

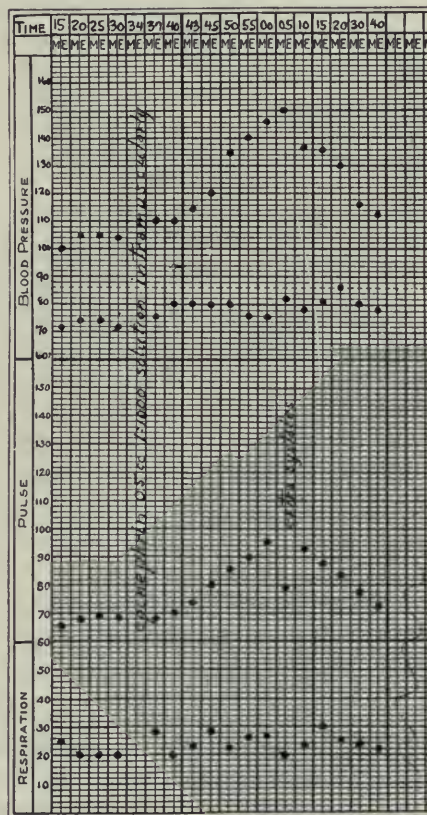


Chart 5.—A definitely positive reaction in an individual (D. C.) with long-standing symptoms of "irritable heart." There is a characteristic sharp rise in systolic blood pressure after a period of nine minutes, with a slight fall in the diastolic blood pressure at the height of the reaction. Associated with the blood pressure changes there is an increase in the pulse from 68 to 94, and the extrasystoles which were present before the administration of the epinephrin, become very numerous.

Although all efforts were made to improve the physical condition of these men, not one of those who gave a positive reaction, and only three who gave negative reactions were able to go to full duty. They

were unable to stand the strain and in addition their reaction to gunfire makes them all the more undesirable for full duty. They are not fit to fight, and even in limited service their value is questionable. This class of patients is not a true product of the war, for they are seen

TABLE 7.—MARKED TREMOR WHICH BECAME GENERALIZED, FLUSHING, MARKED PULSATION, RESTLESSNESS AND PRECORDIAL PAIN INDICATING POSITIVE REACTION (D. C.)

Time	Tremor	Sweating	Flushing	Pulsation	Miscellaneous
8:10	++ coarse	+ palms moist	None	+	Rather restless, occasional extra systoles
9:20	++ arm tremor	+ palms moist	None	in neck	Numerous extra systoles
9:25	++ arm and hand coarse	+ palms moist	None	in neck	Rather restless, extra systoles same
9:30	++ arm and hand coarse	+ palms moist	None	in neck	Rather restless, extra systoles same
9:34*	+++	+	+	+	Chin trembling, restless
9:37	arm trembling	palms moist	+	in neck	Respirations deep, extra systoles same
9:40	+++	+	+	+	
9:43	+++ coarse	+	+	in neck	
9:45	+++ coarse	+	++	++	Respirations not so deep
9:50	+++ whole arm	less	++	++	Restless, neck muscles trembling
9:55	+++ trembling all over	less	++	+++	Precordial pain, neck and arms trembling
10:05	+++	+	++	++	Numerous extra systoles
10:10	++	+	++	++	Numerous extra systoles
10:15	++	+	++	++	Numerous extra systoles
10:20	++	+	++	++	Not so restless
10:32	++	+	++	+	More quiet
10:42	++	+	+	+	Quiet

\* Epinephrin 0.5 c.c. 1:1,000 solution Intramuscularly.

not only in military but also in civilian life. They are of the type who go from one outpatient clinic to another with complaints of nervousness, weakness, palpitation, precordial pain and dyspnea. They are classed as neurotic or neurasthenic individuals and have usually been receiving medical attention for years. As a class they have assumed a new importance since their induction into the army. There seems to be a certain level of strain below which these people can live without their symptoms, and their one effort in life is to keep below this level. Above it their symptoms appear and they break. This explains why they are found in the army as a class and not in civil life as such. In both places, however, they present a problem of no little importance to the internist and to the practitioner of general medicine.

We are glad to take this opportunity to express our thanks to Miss Edna H. Tompkins for her constant assistance in making many of the observations on which this study has been based.

## STUDIES ON EPINEPHRIN. II

THE EFFECTS OF EPINEPHRIN ON THE BASAL METABOLISM IN SOLDIERS  
WITH "IRRITABLE HEART," IN HYPERTHYROIDISM  
AND IN NORMAL MEN \*

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### INTRODUCTION

During a general course of study on the syndrome of the so-called "irritable heart of soldiers," investigation was made into the frequently alleged relationship of this disorder to hyperthyroidism. Among other methods of examination employed in the study was the epinephrin reaction as used by Goetsch.<sup>1</sup> He reports that patients with hyperthyroidism are hypersensitive to epinephrin in that following the injection of the drug a much greater response is obtained than is the case in normal individuals. This response consists in a rise of blood-pressure and pulse rate, and the production of certain characteristic symptoms.

In the investigation at General Hospital No. 9 on patients showing the symptom complex of the "irritable heart of soldiers," it has been found that a considerable percentage of these cases are also hypersensitive to the drug. Careful clinical analysis, however, as well as determinations of the basal metabolism, do not lend any support to the theory that hyperthyroidism is an underlying feature in the condition. It was hoped, therefore, that a study of the basal metabolism under the effects of epinephrin would assist in the explanation not only of why there was a response to the drug in any of the cases of "irritable heart," but further as to why this response was evoked in only a certain percentage of the cases. Incidentally, the opportunity to study

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\* This investigation was suggested by and started under the direction of Major Francis W. Peabody, M. C., U. S. Army, and completed under the direction of Capt. Bertnard Smith, M. C., U. S. Army, at U. S. Army General Hospital No. 9, Lakewood, N. J.

1. Goetsch, E.: *Newer Methods in the Diagnosis of Thyroid Disorders: Pathological and Clinical*, N. Y. State J. M. **18**:259 (July) 1918.

the effects of epinephrin on subjects in whom no unusual reaction was produced by the drug and also on a group of cases who were hypersensitive to it, promised to throw some light on the physiological effect of epinephrin in the organism.

#### REVIEW OF THE LITERATURE

Most studies of the respiratory exchange under the effects of epinephrin have been made more from interest in the resulting carbohydrate mobilization and combustion as illustrated by changes in the respiratory quotient than in the effect on the total metabolism. It is this viewpoint, probably, together with the unsatisfactory valuation to be placed on respiratory quotient figures, which accounts for the few studies concerning the influence of epinephrin on the heat production.

The results of animal experimentation upon the question show absolute disagreement. According to Hari,<sup>2</sup> Welecki found the carbon dioxid and water output lowered after intraperitoneal injection of epinephrin and elevated after intravenous injection. Hari, using curarized animals, found a diminished metabolism under both conditions of injection, although an elevated respiratory quotient. Jackson<sup>3</sup> also reported diminished oxygen intake. Wilenko,<sup>4</sup> working on animals under urethane, found no change in metabolism or respiratory quotient after epinephrin, but at the same time a total absence of the normal rise in both factors on simultaneous carbohydrate feeding. On the other hand, La Franka<sup>5</sup> and Bernstein<sup>6</sup> obtained elevation in the oxygen intake but unchanged quotients, while Lusk<sup>7</sup> showed increase in the respiratory quotient as well as in the metabolism.

The clinical studies, while consistent, are too few in number to allow definite conclusions to be drawn as to the effects of epinephrin on heat output. The reports of both Fuchs and Roth,<sup>8</sup> and of Bern-

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2. Hari, P.: Ueber den Einfluss des Adrenalins auf den Gaswechsel, *Biochem. Ztschr.* **38**:23, 1912.

3. Jackson, D. E.: An Experimental Investigation of Certain Phenomena Relating to the Action of Drugs on the Rate of Oxygen Consumption in the Animal Body, *J. Lab. & Clin. M.* **2**:145 (Dec.) 1916.

4. Wilenko, G. G.: Ueber den Einfluss des Adrenalins auf den Respiratorischen Quotienten und die Wirkungsweise des Adrenalins, *Biochem. Ztschr.* **42**: 44, 1912.

5. La Franka, S.: Untersuchen über den Respiratorischen Stoffwechsel bei Experimenteller Glycosuria, *Ztschr. f. Exper. Path. u. Therap.* **6**:1, 1909.

6. Bernstein, S.: Studien über die Wirkung einzelner Blutdruesen Extrakte in besonders auf den Respiratorischen Stoffwechsel, *Ztschr. f. Exper. Path. u. Therap.* **15**:86, 1914.

7. Lusk, G.: Animal Calorimetry. VIII. The Alleged Influence of the Adrenals on Diabetic Metabolism, *Arch. Int. Med.* **13**:673 (April) 1914.

8. Fuchs, D., and Roth, N.: Untersuchungen über die Wirkung des Adrenalins auf den Respiratorischen Stoffwechsel, *Ztschr. f. Exper. Path. u. Therap.* **10**:187, 1912.

stein and Falta<sup>9</sup> show a decided rise in caloric production and in respiratory quotient on subcutaneous injection of one milligram of epinephrin; but these reports are in total on but seven cases, and those of different types. They are on two cases of acromegaly, one of Addison's disease, one infant and three normal men. They show no distinction between the normal and the pathologic cases.

#### METHODS

Due to this deficiency in clinical data we felt it necessary to study not only the cases of "irritable heart," but a group of normal cases for comparison. For this purpose men with simple organic heart lesions as well as the admittedly normal man seemed a most satisfactory contrast to the "irritable heart" group. Patients with hyperthyroidism, on the other hand, presented the best pathologic contrast.

With the exception of the preliminary rest period, the epinephrin test was conducted essentially along the lines stipulated by Goetsch. Our patients rested in bed for but one to two hours before the test was started. The pulse, blood pressure and respiration readings, together with records of the objective state of the patient—tremor, vasomotor reactions, pulsations—were charted from time to time during this rest period until the records showed a constant level. There was then injected into the deltoid muscle 0.5 c.c. of 1:1,000 "adrenalin" solution, freshly prepared from the tablets as put up by Parke, Davis and Company. The chart readings were then taken every three minutes for several readings, then every five minutes until the end of an hour, and then every ten minutes for one-half hour longer.

A typical response to the injection consists in a rise in systolic blood pressure of at least 10 mm. of mercury, with a concomitant acceleration in pulse rate of at least 10 beats per minute. The diastolic blood pressure may rise, fall or remain unaltered. Parallel with these changes is an increase in certain characteristic signs and symptoms—tremor, vasomotor reactions, palpitation and at times precordial pain. Such, then, are the criteria for the minimum changes that a reaction to the drug must fulfil in order that it may be called "positive" and the patient be considered "epinephrin sensitive."

When these changes are not produced in this characteristic combination and degree, the reaction is regarded as "negative."

Between this group of patients with definitely positive or negative reactions a small number were met with who had to be classified as "questionable reactions."

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9. Bernstein, S., and Falta, W.: Ueber die Einwirkung von Adrenalin, Pituitrinum Infundibulare, und Pituitrinum Glandulare auf den Respiratorischen Stoffwechsel, Verhandl. d. Deutsch. Kongresses f. Inn. Med., Wiesbaden, 1912.

As is described in detail in the general report on the effects of epinephrin in a separate paper,<sup>10</sup> the time interval between the injection and reaction, and the grade and duration of the latter showed variations; but for the purposes of this report it is unnecessary to distinguish further than between positive and negative reactions.

The metabolism was determined by the Tissot method. A 100 liter spirometer was used in connection with a half mask covering nose and mouth. The analyses of the expired air were made on the portable Haldane gas analysis apparatus. Values for the respiratory rate and depth were based on pneumographic records of the respiration. All volumes were computed in the standard way. The calorific production was obtained by indirect calorimetry as the method implies. It was computed from the nonprotein respiratory quotient. Nitrogen analyses were not made. The heat production per square meter of body surface was based on the height-weight formula of DuBois,<sup>11</sup> and the standards of metabolism for varying ages as established by DuBois and associates.

All periods were from nine to ten minutes in duration with the exception of rare instances when the spirometer was filled too rapidly to permit of so long a period. All patients had been fasting from twelve to fourteen hours. All received two independent basal determinations as a base line for later changes in metabolism.

The first basal period was obtained after the patient had been at rest until the pulse showed a constant level. The second basal determination was made with a new placement of the mask, and after the performance of any disturbing factors which the requirements of the complete study would later necessitate. These included blood pressure readings, venepuncture for blood sugar analyses, blood smears and electrocardiographic studies. We, therefore, feel that two agreeing basal periods under these conditions assure not only a satisfactory base line from which to judge later metabolic changes, but also assure that such metabolic changes are due to the epinephrin and not to other factors.

If a metabolic determination was to be started within five minutes of the epinephrin injection, the mask was not removed after the second basal period. Also it was not removed when periods started within fifteen minutes of each other. Otherwise, it was replaced for all periods.

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10. Wearn, J. T., and Sturgis, C. C.: Effects of the Injection of Epinephrin in Soldiers with "Irritable Heart." *Arch. Int. Med.*, this issue, p. 247.

11. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area If Height and Weight Be Known, *Arch. Int. Med.* **17**: 863 (June) 1916.

12. Aub, J. C., and Du Bois, E. F.: The Basal Metabolism of Old Men, *Arch. Int. Med.* **19**:823 (June) 1917.

The beginning of metabolism periods subsequent to the injection depended largely upon the patient's response to the drug. In cases that gave a positive reaction, the metabolism was determined as nearly as possible at the height of the reaction, as well as at some time before and after this point. In the negative cases any index of metabolic disturbance was, of course, lacking. Determinations were thus made on a time comparison with the positive cases—about thirty minutes after the injection. Here, also, they were made at various times before and after that.

#### PRESENTATION OF DATA

Four groups of subjects have been studied. Two of these groups were "epinephrin negative" and showed no reaction, while two were "epinephrin positive" and responded with the typical reaction of the hypersensitive subject. The "epinephrin negative" groups consisted of normal subjects, and of patients with "effort syndrome" who did not react to epinephrin. The "epinephrin positive" groups consisted of patients with "effort syndrome" who reacted to epinephrin and a small series of cases of hyperthyroidism. Tables 1, 2, 3 and 4 give simply the hospital records and detailed metabolic data of these groups. Tables 5, 6, 7 and 8 tabulate the salient metabolic findings in relation to epinephrin reaction. In these tables, only the average values of the two basal periods have been given. They are represented by periods 1 and 2. Our limit for satisfactory agreement in the percentage normality of the metabolism in two basal periods is a variation of 3 per cent. Any cases showing a greater disagreement than this are starred. Of these, none disagree by more than 6 per cent.

The pulse and blood pressure readings are the average values charted over the duration of the metabolic determination, nine minutes. The presence of subjective symptoms more intense than in the basal determinations is noted by a plus sign.

#### DISCUSSION OF RESULTS

With unbroken regularity the metabolism shows a rise after the injection of epinephrin. This is true in the normal as well as in the pathological cases. It is true whether there is any other sign of reaction or not. This increase in metabolism, however, is far more marked in those cases with a positive than in those with a negative reaction. With but one exception (Case 7, Table 1) every positive reaction was accompanied by a rise in metabolism of 20 per cent. or over. On the other hand, no negative reaction shows a rise above 20 per cent., and on the whole not above 15 per cent.

TABLE 1.—METABOLISM DETERMINATIONS ON "EPINEPHRIN POSITIVE" PATIENTS WITH "IRRITABLE HEART"

Case No.	Name	Register No.	Date	Age	Height, Cm.	Weight, Kg.	Rectal Temp., F.	Metabolism										
								Period No.	Minutes from Injection to Start	CO <sub>2</sub> per Min. C.e.	O <sub>2</sub> per Min. C.e.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P.	Volume per Respiration, C.e.	Calories per Square Meter per Hour	Metabolism per Cent. Normal
1	G. A.	729	Aug. 27	24	174	68.2	97.4	1-2 3 4 5	... 2 41 96	203 236 251 195	254 276 332 252	0.81 0.85 0.75 0.77	78 103 124 90	15.6 17.5 17.4 19.9	5.47 6.48 7.09 6.10	348 370 408 306	40.1 44.0 51.7 39.4	+2 +11 +31 ±0
2	F. B.	1146	Aug. 24	31	181	70.1	98.3	1-2 3 4	... 10 30	218 237 311	266 297 339	0.82 0.86 0.92	75 84 108	17.9 16.7 19.3	6.45 7.11 8.57	361 425 445	38.7 43.7 50.7	-3 +11 +28
3	H. B.	1143	Sept. 4	20	170	57.7	98.2	1-2 3 4 5	... 3 39 87	184 214 225 192	237 241 254 257	0.78 0.89 0.78 0.75	59 66 71 66	17.6 17.8 19.5 14.7	5.38 6.12 6.86 5.49	306 343 352 373	40.6 42.5 49.2 43.3	+3 +8 +25 +10
4	D. C.	2395	Aug. 30	26	177	63.0	97.8	1-2 3 4	... 3 31	231 232 275	272 291 335	0.85 0.87 0.82	68 73 85	16.9 19.7 18.3	6.15 6.66 7.75	365 337 424	44.6 47.9 54.6	+13 +21 +38
5*	F. E.	2581	Sept. 23	21	165	56.8	97.4	1-2 3	... 29	135 178	193 251	0.71 0.71	72 87	13.0 15.5	3.59 4.92	276 318	33.4 43.4	-16 +10
6	J. F.	423	Sept. 3	23	172	58.2	...	1-2 3 4 5	... 2 26 88	184 207 268 217	227 242 290 250	0.81 0.85 0.92 0.87	71 71 90 72	21.7 21.4 24.3 22.1	6.25 6.71 9.08 7.74	280 314 374 350	38.9 42.1 51.2 43.6	-2 +7 +30 +10
7	W. H.	934	Aug. 9	30	167	51.4	98.5	1-2 3 4 5	... 18 33 74	164 202 290 132	189 214 219 184	0.87 0.94 0.91 0.71	60 74 73 65	14.8 16.7 17.8 16.0	4.45 5.62 5.76 3.99	301 336 324 249	35.3 40.6 41.4 33.0	-11 +3 +5 -16
8	K. K.	1226	Aug. 29	23	173	61.9	...	1-2 3 4	... 1 35	180 243 180	232 256 288	0.78 0.95 0.63	97 123 124	14.5 18.8 18.1	4.92 6.91 5.78	341 367 319	38.2 44.0 46.5	-4 +11 +18
9	F. K.	1097	Aug. 10	26	171	52.9	...	1-2 3 4 5 6	... 19 36 94 110	178 216 213 193 190	220 260 269 254 245	0.81 0.83 0.79 0.76 0.78	73 92 90 84 82	21.5 21.6 21.3 22.2 21.2	5.77 6.70 6.68 6.19 5.97	268 310 314 279 282	37.6 44.7 45.7 42.8 41.5	-5 +13 +16 +8 +5
10*	J. K.	1177	Aug. 17	31	166	59.8	...	1-2 3 4	... 20 65	181 237 185	236 294 255	0.77 0.81 0.73	64 75 76	23.5 21.3 20.0	5.72 7.08 5.69	244 333 284	40.4 50.8 43.3	+2 +29 +10
11	E. McC.	707	Aug. 13	20	172	63.6	98.2	1-2 3 4 5	... 10 33 78	175 197 218 186	213 242 269 197	0.82 0.81 0.81 0.94	... ... ... ...	12.9 14.1 15.7 11.0	4.62 5.07 5.83 4.81	390 359 371 435	35.1 39.8 44.2 33.3	-12 +1 +12 -16
12	J. S.	870	Aug. 22	24	164	69.1	...	1-2 3 4 5	... 10 34 67	286 293 392 321	266 284 336 300	1.08 0.93 0.90 1.07	79 76 100 84	15.4 15.9 18.9 16.2	9.27 8.90 9.93 10.27	600 559 524 633	45.8 48.0 54.3 51.6	+16 +22 +43 +31
13*	F. S.	721	Aug. 19	23	173	63.4	98.8	1-2 3 4 5	... 21 55 83	235 271 263 236	285 325 324 286	0.83 0.81 0.81 0.82	65 75 68 72	45.7 58.3 63.8 58.7	10.80 14.56 15.22 14.74	237 250 238 251	46.6 54.7 52.9 46.8	+18 +38 +34 +18

TABLE 2.—METABOLISM DETERMINATIONS ON "EPINEPHRIN POSITIVE" PATIENTS WITH HYPERTHYROIDISM

Case No.	Name	Register No.	Date	Age	Height, Cm.	Weight, Kg.	Buccal Temp., F.	Metabolism										
								Period No.	Minutes from Injection to Period Start	CO <sub>2</sub> per Min. C.e.	O <sub>2</sub> per Min. C.e.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. l	Volume per Respiration, C.e.	Calories per Square Meter per Hour	Metabolism per Cent. from Normal
32	R. J.	2410	Aug. 6	27	166	50.0	99.0	1-2	...	256	344	0.75	...	19.8	7.66	388	63.4	+61
								3	10	313	380	0.83	133	21.3	9.21	432	71.6	+81
								4	26	290	380	0.76	134	21.3	8.94	420	70.3	+78
33	T. M.	851	Aug. 16	19	173	64.3	....	1-2	...	280	358	0.80	94	18.0	7.22	462	58.2	+42
								3	12	365	425	0.86	120	18.2	9.12	501	70.2	+71
								4	41	365	424	0.86	122	19.5	9.61	492	70.0	+71
								5	91	331	397	0.83	119	17.9	8.70	487	65.2	+59
34	E. S.	896	Oct. 25	27	185	72.5	99.2	1-2	...	284	364	0.78	109	19.1	8.46	444	53.4	+35
								3	6	422	440	0.96	130	18.6	11.68	628	67.7	+71
								4	31	333	428	0.78	137	18.1	9.99	553	62.8	+59

TABLE 3.—METABOLISM DETERMINATIONS ON "EPINEPHRIN NEGATIVE" PATIENTS WITH "IRRITABLE HEART"

Case No.	Name	Register No.	Date	Age	Height, Cm.	Weight, Kg.	Buccal Temp., F.	Metabolism										
								Period No.	Minutes from Injection to Period Start	CO <sub>2</sub> per Min. C.c.	O <sub>2</sub> per Min. C.c.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P.	Volume per Respiration, C.c.	Calories per Square Meter per Hour	Metabolism per Cent. from Normal
14	N. A.	2327	Nov. 7	32	183	72.3	97.6	1-2 3 4	... 5 32	242 258 263	278 299 320	0.87 0.86 0.82	58 65 64	17.5 17.6 19.6	7.50 7.90 8.55	429 440 436	42.0 45.1 47.7	+ 7 +14 +21
15	A. C.	2194	Oct. 24	25	177	60.5	....	1-2 3 4	... 5 31	231 259 247	274 288 285	0.85 0.90 0.86	84 89 90	16.0 18.1 19.0	6.44 7.44 7.49	404 411 394	45.7 48.6 47.7	+16 +23 +21
16*	F. C.	2171	Oct. 31	25	166	56.4	98.2	1-2 3 4	... 5 35	188 206 205	242 251 267	0.78 0.82 0.77	74 77 77	6.5 8.5 7.3	4.28 4.91 4.83	637 575 663	42.8 44.9 47.2	+ 9 +14 +19
17	E. G.	1069	Oct. 7	24	165	55.5	98.7	1-2 3	... 18	158 184	204 225	0.77 0.82	74 89	11.0 9.9	4.18 4.70	380 476	35.9 40.1	- 9 + 2
18	L. J.	1628	Aug. 23	23	174	65.0	....	1 2 3 4	... 8 40 76	186 200 187 179	226 248 247 235	0.82 0.81 0.76 0.76	72 71 76 70	17.7 18.9 19.1 18.1	5.08 5.61 5.57 5.04	288 297 292 279	36.7 40.3 39.5 37.6	- 7 + 2 ± 0 ± 5
19	J. L.	2484	Aug. 7	29	168	64.1	98.2	1-2 3 4	... 15 31	208 251 252	256 289 291	0.81 0.87 0.87	69 71 75	28.8 36.3 38.1	6.91 8.70 9.03	222 240 237	42.5 48.7 49.0	+ 8 +23 +24
20	R. L.	1971	Nov. 4	23	175	61.1	....	1-2 3 4	... 5 34	181 190 192	231 233 247	0.78 0.81 0.77	69 73 72	10.1 10.7 11.1	4.31 4.33 4.69	430 405 422	37.8 38.5 40.4	- 5 - 3 + 2
21	M. H.	1104	Aug. 8	23	168	63.4	98.4	1-2 3 4	... 22 39	170 200 151	216 236 188	0.79 0.85 0.80	61 71 70	24.8 22.8 23.1	5.66 6.42 4.83	229 281 209	35.7 39.5 31.1	-10 ± 0 -21
22	O. N.	1243	Oct. 19	29	166	60.2	98.8	1-2 3	... 33	204 211	250 268	0.82 0.79	72 80	18.0 18.8	6.00 6.21	334 330	43.3 46.1	+10 +17
23	M. T.	2820	Jan. 24	25	172	63.2	97.4	1-2 3 4	... 16 31	178 227 190	222 262 243	0.80 0.87 0.78	52 58 64	.... .... ....	4.82 5.79 4.79	... ... ...	36.6 43.9 39.8	- 8 +11 + 1
24	I. Z.	1230	Aug. 21	22	177	60.2	....	1-2 3 4	... 5 39	187 209 205	232 248 248	0.81 0.84 0.83	72 71 72	12.8 13.8 14.4	4.38 5.13 5.49	342 372 381	38.4 41.4 41.3	- 3 + 5 + 5
25	D. Z.	2195	Nov. 1	22	191	73.0	98.2	1-2 3 4	... 5 35	257 273 277	303 312 329	0.85 0.87 0.84	71 71 70	18.3 20.0 20.5	7.23 7.24 7.83	396 362 382	44.2 45.7 47.9	+12 +16 +21

TABLE 4.—METABOLISM DETERMINATIONS ON "EPINEPHRIN NEGATIVE" PATIENTS—ALL NORMAL MEN

Case No.	Name	Register No.	Date	Age	Height, Cm.	Weight, Kg.	Buccal Temp., F.	Metabolism										
								Period No.	Minutes from Injection to Period Start	CO <sub>2</sub> per Min. C.c.	O <sub>2</sub> per Min. C.c.	R. Q.	Pulse	Respiration	Volume per Min. S. D. Min. T. P. 1	Volume per Respiration, C.c.	Calories per Square Meter per Hour	Metabolism per Cent. from Normal
26	F. B.	1244	Oct. 3	29	183	84.1	....	1-2 3	... 31	235 267	272 293	0.87 0.91	56 58	13.9 16.4	5.79 6.97	476 426	38.6 42.2	- 3 + 7
27	G. F.	2241	Oct. 30	20	168	62.7	98.8	1-2 3 4	... 4 34	211 229 233	241 241 257	0.87 0.95 0.91	74 75 82	16.7 17.5 17.9	5.43 6.02 6.17	324 345 346	41.3 42.2 44.5	+ 5 + 7 + 13
28*	W. J.	813	Sept. 9	24	174	64.5	....	1-2 3 4 5	... 3 39 96	202 222 215 200	248 250 275 235	0.82 0.89 0.78 0.85	63 64 63 71	9.6 14.3 10.9 9.6	4.98 5.91 5.80 5.22	521 412 534 543	40.3 41.4 44.3 38.5	+ 2 + 5 + 12 - 3
29	J. K.	1618	Sept. 6	23	180	68.6	97.6	1-2 3 4 5	... 2 37 84	170 181 191 149	224 229 232 219	0.77 0.79 0.76 0.68	66 70 69 66	12.0 12.0 12.1 11.0	4.67 4.98 5.20 4.06	389 415 430 371	34.2 35.2 38.5 32.9	- 14 - 11 - 3 - 17
30	R. L.	2556	Oct. 18	18	183	80.0	99.2	1-2 3	... 36	204 273	328 349	0.81 0.78	77 75	22.8 23.1	7.58 7.04	333 305	46.6 49.2	+ 14 + 20
31	J. R.	2160	Nov. 16	33	176	66.6	98.2	1-2 3 4	... 3 34	231 256 225	280 296 298	0.83 0.87 0.75	71 66 65	11.1 11.3 11.5	6.31 7.00 6.19	568 621 541	44.6 47.7 46.6	+ 13 + 21 + 18

The two basal periods disagreed between 3 and 6 per cent.

TABLE 5.—CORRELATION OF METABOLIC AND REACTION DATA ON "EPINEPHRIN POSITIVE" PATIENTS WITH "IRRITABLE HEART"

Case No. and Name	Period No.	Minutes from Injection to Period Start	Metabolism per Cent. from Normal	Amount of Metabolic Rise, per Cent.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Reaction		
									Systolic Blood Pressure, Mm.	Diastolic Blood Pressure, Mm.	Symptoms
1 G. A.	1-2	..	+ 2	....	0.81	78	15.6	5.47	109	85	
	3	2	+11	+ 9	0.85	103	17.5	6.48	116	85	+
	4	41	+31	+29	0.75	124	17.4	7.09	144	100	++
	5	96	+ 0	- 2	0.77	90	19.9	6.10	110	94	
2 F. B.	1-2	..	- 3	....	0.82	75	17.9	6.45	118	80	
	3	10	+11	+14	0.86	84	16.7	7.11	120	79	+
	4	30	+28	+31	0.92	108	19.3	8.57	143	88	++
3 H. B.	1-2	..	+ 3	....	0.78	59	17.6	5.38	97	66	
	3	3	+ 8	+ 5	0.89	66	17.8	6.12	105	69	+
	4	39	+25	+22	0.78	71	19.5	6.86	114	64	+
	5	87	+10	+ 7	0.75	66	14.7	5.49	96	60	
4 D. C.	1-2	..	+13	....	0.85	68	16.9	6.15	104	74	
	3	3	+21	+ 8	0.87	73	19.7	6.66	113	78	++
	4	31	+38	+25	0.82	85	18.3	7.75	143	79	++
5 F. E.	1-2	..	-16	....	0.71	72	13.0	3.59	109	80	
	3	29	+10	+26	0.71	87	15.5	4.92	125	78	+
6 J. F.	1-2	..	- 2	....	0.81	71	21.7	6.25	126	90	
	3	2	+ 7	+ 9	0.85	71	21.4	6.71	129	94	
	4	26	+30	+32	0.92	90	24.3	9.08	155	97	+
	5	88	+10	+12	0.87	72	22.1	7.74	129	90	
7 W. H.	1-2	..	-11	....	0.87	60	14.8	4.45	100	75	
	3	18	+ 3	+14	0.94	74	16.7	5.62	113	79	
	4	33	+ 5	+16	0.91	73	17.8	5.76	119	82	++
	5	74	-16	- 4	0.71	65	16.0	3.99	107	79	
8 K. K.	1-2	..	- 4	....	0.78	97	14.5	4.92	131	96	
	3	1	+11	+15	0.95	123	18.8	6.91	142	99	+
	4	35	+18	+22	0.63	124	18.1	5.78	142	87	++
9 F. K.	1-2	..	- 5	....	0.81	73	21.5	5.77	113	86	
	3	19	+13	+18	0.83	92	21.6	6.70	122	91	
	4	36	+16	+21	0.79	90	21.3	6.68	127	87	+
	5	94	+ 8	+13	0.76	84	22.2	6.19	120	90	
10 J. K.	1-2	..	+ 2	....	0.77	64	23.5	5.72	115	83	
	3	20	+29	+27	0.81	75	21.3	7.08	124	85	
	4	65	+10	+ 8	0.73	76	20.0	5.69	115	90	
11 E. McC.	1-2	..	-12	....	0.82	...	12.9	4.62			
	3	10	+ 1	+13	0.81	...	14.1	5.07			
	4	33	+12	+24	0.81	...	15.7	5.83			
	5	78	-16	- 4	0.94	...	11.0	4.81			
12 J. S.	1-2	..	+16	....	1.08	79	15.4	9.27	133	100	
	3	10	+22	+ 6	0.93	76	15.9	8.90	126	86	
	4	34	+43	+27	0.90	100	18.9	9.98	158	95	+
	5	67	+31	+15	1.07	84	16.2	10.27	129	98	
13 F. S.	1-2	..	+18	....	0.83	65	45.7	10.80	143	108	
	3	21	+38	+20	0.81	75	58.3	14.56	149	94	
	4	55	+34	+16	0.81	68	68.8	15.22	132	94	
	5	83	+18	± 0	0.82	72	58.7	14.74	120	102	

This increase in the metabolism is expressed partly by a greater oxygen deficit in the expired air, but far more by an increased amount of air breathed as is shown by the greatly augmented minute volumes. This increase in the minute volume is as invariable as is the rise in metabolism. The amount of air breathed per minute was increased as much as two liters in a considerable number of cases.

This response in minute volume is generally, but not invariably, dependent upon increase in both rate and depth of respiration. In a number of cases, however, only one of these factors responded. This is especially true in the subjects with a negative reaction. In those with a positive reaction, regardless of whether rate changed, depth of respiration was consistently augmented with one interesting exception (Case 13, Table 1), who was already breathing at a rate which tended to preclude increase in depth.

TABLE 6.—CORRELATION OF METABOLIC AND REACTION DATA ON "EPINEPHRIN POSITIVE" PATIENTS WITH HYPERTHYROIDISM

Case No. and Name	Period No.	Minutes from Injection to Period Start	Metabolism per Cent. from Normal	Amount of Metabolic Rise, per Cent.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Reaction		
									Systolic Blood Pressure, Mm.	Diastolic Blood Pressure, Mm.	Symptoms
32 R. J.	1-2	..	+61	....	0.75	...	19.8	7.66			
	3	10	+81	+20	0.83	133	21.3	9.21			
	4	26	+78	+17	0.76	134	21.3	8.94			
33 T. M.	1-2	..	+42	....	0.80	94	18.0	7.22	126	85	
	3	12	+71	+29	0.86	120	18.2	9.12	147	91	++
	4	41	+71	+29	0.86	122	19.5	9.61	147	95	+
	5	91	+59	+17	0.83	119	17.9	8.70	135	88	+
34 E. S.	1-2	..	+35	....	0.78	109	19.1	8.46	131	74	
	3	6	+71	+36	0.96	130	18.6	11.63	154	71	++
	4	31	+59	+24	0.78	137	18.1	9.99	149	62	+

In the positive cases one metabolism period was taken as nearly as possible at the height of the epinephrin reaction, and it was at this point that the greatest metabolic increase was found. Since, however, the periods during which the metabolism was determined were at the height of the reaction and not immediately before and after the apex, one cannot decide definitely whether the caloric elevation shortly precedes or occurs simultaneously with the reaction changes. It can merely be stated that there is a large metabolic increase during the period of maximum change in pulse, blood pressure and symptoms; and that there is a direct relationship between this increase and the reaction changes. It can in no way be stated that the increase is due to the changes.

For a satisfactory comparison with the positive cases, it was necessary in the negative cases, due to the absence of any reaction, to take a metabolism period at a time interval following the injection which synchronized with the maximum point of reaction in the hypersensitive cases. Under these conditions, the negative cases, while never giving a metabolic response equal to that at the apical point of the positive cases, showed a tendency to reach their maximum of change at a period earlier than the time of apical change in the positive cases.

This necessitates reiteration of the fact that the maximum metabolic increase in the "epinephrin sensitive" cases may also occur before the time of apical reaction change.

TABLE 7.—CORRELATION OF METABOLIC AND REACTION DATA ON "EPINEPHRIN NEGATIVE" PATIENTS WITH "IRRITABLE HEART"

Case No. and Name	Period No.	Minutes from Injection to Period Start	Metabolism per Cent. from Normal	Amount of Metabolic Rise, per Cent.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. F. 1	Reaction		
									Systolic Blood Pressure, Mm.	Diastolic Blood Pressure, Mm.	Symptoms
14 N. A.	1-2	..	+ 7	....	0.87	58	17.5	7.50	123	75	
	3	5	+14	+ 7	0.86	65	17.6	7.90	133	66	
	4	32	+21	+14	0.82	64	19.6	8.55	148	62	
15 A. C.	1-2	..	+16	....	0.85	84	16.0	6.44	142	84	
	3	5	+23	+ 7	0.90	89	18.1	7.44	146	81	
	4	31	+21	+ 5	0.86	90	19.0	7.49	161	76	
16 F. C.	1-2	..	+ 9	....	0.78	74	6.5	4.28	136	80	
	3	5	+14	+ 5	0.82	77	8.5	4.91	136	75	Slight
	4	35	+19	+10	0.77	77	7.3	4.83	136	72	Slight
17 E. G.	1-2	..	- 9	....	0.77	74	11.0	4.18	97	70	
	3	18	+ 2	+11	0.82	89	9.9	4.70	102	67	
18 L. J.	1	..	- 7	....	0.82	72	17.7	5.08	110	78	
	2	8	+ 2	+ 9	0.81	71	18.9	5.61	115	75	
	3	40	± 0	+ 7	0.76	76	19.1	5.57	118	75	Slight
	4	76	- 5	+ 2	0.76	70	18.1	5.04	113	77	Slight
19 J. L.	1-2	..	+ 8	....	0.81	69	28.8	6.91	104	72	
	3	15	+23	+15	0.87	71	36.3	8.70	111	73	
	4	31	+24	+16	0.87	75	38.1	9.03	103	73	
20 R. L.	1-2	..	- 5	....	0.78	69	10.1	4.31	139	90	
	3	5	- 3	+ 2	0.81	73	10.7	4.33	149	86	Slight
	4	34	+ 2	+ 7	0.77	72	11.1	4.69	146	79	
21 M. H.	1-2	..	-10	....	0.79	61	24.8	5.66	107	75	
	3	22	± 0	+10	0.85	71	22.8	6.42	104	68	
	4	39	-21	-11	0.80	70	23.1	4.83	106	66	
22 O. N.	1-2	..	+10	....	0.82	72	18.0	6.00	129	86	
	3	33	+17	+ 7	0.79	80	18.8	6.21	120	71	
23 M. T.	1-2	..	- 8	....	0.80	52	....	4.82	101	65	
	3	16	+11	+19	0.87	58	....	5.79	115	59	Slight
	4	31	+ 1	+ 9	0.78	64	....	4.79	111	58	
24 I. Z.	1-2	..	- 3	....	0.81	72	12.8	4.38	123	95	
	3	5	+ 5	+ 8	0.84	71	13.8	5.13	126	90	Slight
	4	39	+ 5	+ 8	0.83	72	14.4	5.49	130	90	Slight
25 D. Z.	1-2	..	+12	....	0.85	71	18.3	7.23	136	70	
	3	5	+16	+ 4	0.87	71	20.0	7.24	143	68	
	4	35	+21	+ 9	0.84	70	20.5	7.83	150	70	Slight

Any interpretations to be based on changes in the respiratory quotient must always be made with due consideration of the mechanical factors that may influence the quotient in periods as short as those in the Tissot method. With these factors in mind, we were inclined to disregard the respiratory quotient in this report as of any value in showing changes in the percent usage of the foodstuffs. But a careful analysis of the tables shows such a total disregard as unjustified. In a large percentage of the cases after injection, the respiratory quotient

shows an increase over the basal value. And this increase very frequently occurs before the maximal changes in respiratory volumes and metabolism. Fuchs and Roth<sup>8</sup> noted this same fact. A changing depth of expiration could, of course, account for this. However, the very facts that this change in the quotient occurred before the time of deepest respiration, that it also often shows in periods long enough after the injection for lung adjustment to have taken place, and finally, that it often persists above basal values for some time, would argue against simple pumping out of carbon dioxid as the cause of the elevation. The elevation must be considered as significant of increased combustion of carbohydrate. Furthermore, the hyperglycemia shown by others after epinephrin injection and found in these cases by us, together with the increased metabolism, give even more significance to the rise in respiratory quotient as indicative of stimulated carbohydrate combustion.

TABLE 8.—CORRELATION OF METABOLIC AND REACTION DATA ON "EPINEPHRIN NEGATIVE" PATIENTS—ALL NORMAL MEN

Case No. and Name	Period No.	Minutes from Injection to Period Start	Metabolism per Cent. from Normal	Amount of Metabolic Rise, per Cent.	R. Q.	Pulse	Respiration	Volume per Min. S. D. T. P. 1	Reaction		
									Systolic Blood Pressure, Mm.	Diastolic Blood Pressure, Mm.	Symptoms
26 F. B.	1-2	..	- 3	....	0.87	56	13.9	5.79	120	79	+
	3	31	+ 7	+10	0.91	58	16.4	6.97	125	74	
27 G. F.	1-2	..	+ 5	....	0.87	74	16.7	5.43	134	89	
	3	4	+ 7	+ 2	0.95	75	17.5	6.02	132	82	
	4	34	+13	+ 8	0.91	82	17.9	6.17	138	78	
28 W. J.	1-2	..	+ 2	....	0.82	63	9.6	4.98	102	68	
	3	3	+ 5	+ 3	0.89	64	14.2	5.91	102	70	
	4	39	+12	+10	0.78	63	10.9	5.80	116	69	
	5	96	- 3	- 5	0.85	71	9.6	5.22	112	69	
29 J. K.	1-2	..	-14	....	0.77	66	12.0	4.67	113	83	
	3	2	-11	+ 3	0.79	70	12.0	4.98	113	84	
	4	37	- 3	+11	0.76	69	12.1	5.20	116	77	
	5	84	-17	- 3	0.68	66	11.0	4.06	114	79	
30 R. L.	1-2	..	+14	....	0.81	77	22.8	7.58	134	82	+
	3	36	+20	+ 6	0.78	75	23.1	7.04	140	69	
31 J. R.	1-2	..	+13	....	0.83	71	11.1	6.31	120	80	
	3	3	+21	+ 8	0.87	66	11.3	7.00	123	80	
	4	34	+18	+ 5	0.75	65	11.5	6.19	118	78	

These various metabolic changes bring up two questions—namely, why is there a rise in metabolism after epinephrin injection, and why is this rise so definitely greater in certain subjects than in others?

In consideration of the first question, as to why there is a metabolic increase after epinephrin injection, one may consider a number of possibilities. The much discussed activity of heart and lungs is perhaps to be taken into account. We have shown, however, in cases

of "irritable heart" that normally there may often be an increase in respiratory activity as great as any seen under the effects of epinephrin without changes in the basal metabolism.<sup>13</sup> In regard to the pulse activity, it is to be noted that the "negative" epinephrin reactions, while showing, to be sure, slight increase in the respiratory activity, showed often no pulse acceleration and yet definite metabolic stimulation. As a further study of the effect of pulse acceleration on the metabolism, we made determinations, which are to be published later, on a number of both "epinephrin positive" and "negative" cases after the injection of 1.2 mg. atropin. In both cases the pulse rate showed increases greater than was general in "positive" epinephrin reactions, and yet there was no metabolic rise. Therefore, respiration and heart activity cannot account for the general rise in metabolism under epinephrin, though it might possibly be responsible in a slight degree for the grade of increase in the positive cases. In fact, the increase in metabolism is more conceivably the cause for increased respiratory and circulatory activity than vice versa.

The excitement attendant on injection might be considered the cause for metabolic increase. In opposition to this there are two facts — first, the rise in metabolism is greater some time after the injection than immediately following it, and secondly, we carried out control determinations upon positive cases, patients with hyperthyroidism and normal men after the injection of sterile water and found no change in metabolism.

As mentioned above, one of the objective symptoms of the epinephrin reaction is tremor. In the negative cases little gross tremor is visible, but there may be a general increase of muscular tonus, and this might account for a rise in oxygen consumption.

Another possible cause for the rise in metabolism is the hyperglycemia due to the action of epinephrin. This has been considered by practically every experimenter in the field. Carbohydrate plethora results in increased metabolism, which is at the expense of the carbohydrate as shown by the simultaneous elevation of the respiratory quotient. The elevation in the metabolism and the respiratory quotient under epinephrin can thus very plausibly be attributed to the known hyperglycemia resulting from the epinephrin.

All previous experimenters have also discussed the possibility of epinephrin as a direct stimulant to cellular metabolism in general. With regard to this contention there is little evidence one way or the other at the present time. It is, however, generally accepted that

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13. Peabody, F. W., Wearn, J. T., and Tompkins, E. H.: The Basal Metabolism in Cases of True "Irritable Heart" of Soldiers, *Med. Clin. of North America* 2:507, 1918.

epinephrin has a definitely selective action on the sympathetic autonomic nervous system. It is probable, therefore, that the epinephrin acts indirectly in causing an increase in the metabolism, and it is by acting through the sympathetic system that it produces the changes—the tremor, hyperglycemia, etc.—which are probably the actual causes of the increased heat output.

And it is probably in this selective action of the epinephrin on the sympathetic autonomic nervous system that an explanation is to be sought for the differences of response to a given injection of epinephrin in the individuals with the “irritable heart” syndrome. A difference in the sensitivity of the system to the drug possibly accounts for the differences in response of the individuals studied.

#### CONCLUSIONS

1. Intramuscular injection of epinephrin causes an increase in total gaseous metabolism in normal men, patients with “irritable heart” and in hyperthyroidism.

2. The increase in metabolism is greater in cases showing a “positive” reaction to the epinephrin than in those showing no characteristic reaction, and it is parallel to the pulse, blood pressure and symptomatic changes.

3. There is an increase in the minute volume of air breathed under the effects of epinephrin, and of either respiratory rate or depth, or both.

4. After intramuscular injection of epinephrin there is very frequently an elevation of respiratory quotient. The maximum of this elevation ordinarily precedes that of the metabolic increase.

5. The increase in metabolism is due to some factor other than the excitement attendant on injection or the stimulation to heart and respiratory muscles resulting from injection.

6. The increase in metabolism may be due to increased muscular tonus, or to hyperglycemia. It may be that these factors are only partial expressions of a general indirect stimulus to the metabolism from the epinephrin by its action on some system capable of direct metabolic activation.

7. As epinephrin is a stimulant to the sympathetic autonomic nervous system, the differences in reaction and metabolic response in the negative and positive cases are probably due to differences in that system.

## STUDIES ON EPINEPHRIN. III

### EFFECT OF EPINEPHRIN ON THE ELECTROCARDIOGRAMS OF PATIENTS WITH "IRRITABLE HEART"

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#### INTRODUCTION AND METHODS

This electrocardiographic study was stimulated by the observation of the effect of epinephrin on "irritable heart" cases. In a number of these cases (about 60 per cent.), from twenty to fifty minutes after the injection was made very pronounced changes were induced. There was considerable rise in blood pressure and pulse rate, the patients became dyspneic, complained of precordial pain and dizziness, their hands became cold and tremulous, they became conscious of palpitation, etc.—in a word they seemed to be suffering from the sort of symptoms which had been the original cause for admission to the hospital. In normal trained soldiers this injection produced changes which were essentially negligible.

On account of the effect of epinephrin on the circulation it seemed desirable to find out whether electrocardiographic tracings would show any changes during the occurrence of these symptoms. About eighteen cases of "irritable heart" were studied. The first eight were studied in conjunction with metabolism studies made by Lieut. Joseph T. Wearn, M. C., U. S. A., and Miss Edna H. Tompkins. The tracings, in general, showed a number of different abnormalities which are reported below. A special series of twelve cases was then studied to work out in detail the electrocardiographic changes which might be produced by the drug. Another series of twelve normal men was then studied under identical conditions. The following tabulation contains a classification of the various abnormalities which were found in the electrocardiograms taken at the height of the epinephrin reaction in the first group of eight cases:

#### TYPES OF CHANGE NOTED AFTER EPINEPHRIN

##### 1. Changes in the P-wave:

- (a) General lowering of wave in all leads.
- (b) Sinus arrhythmias which have been seen before the injection have become very pronounced after the injection.
- (c) Inversion of P-wave and return to normal in the same record.
- (d) Interpolated P-wave.

2. Changes in Conduction:
  - (a) Delayed conduction.
  - (b) Partial heart block.
3. Changes in T-Wave:
  - (a) General lowering of wave in all leads.
  - (b) Diphasic T-wave.
  - (c) Inverted T-wave.
4. Effect on Ventricular Muscle:
  - (a) Cases showing occasional extrasystoles before injection have shown showers of them after injection.
  - (b) Extrasystoles induced in cases which normally have shown none.
5. Changes in Heart Rate:
  - (a) Rate at the conclusion has been lower than in the first normal tracing.

These eight cases were not the subject of systematic electrocardiographic study. It was only when the observer noted gross cardiac irregularities that records were made. The changes observed, however, were so striking that they led to a further detailed study of the effect of epinephrin on the electrocardiogram. Twelve men who were hypersensitive to epinephrin were next studied, and in conjunction with these twelve normal men in whom the injection of epinephrin produced no reaction were studied.

TABLE 1.—“IRRITABLE HEART” CASES. BLOOD PRESSURE AND PULSE CHART

Initials	Normal Systolic Pressure*	Systolic Pressure at Height of Reaction	Time for Rise, Min.	Normal Diastolic Pressure*	Diastolic Pressure at Height of the Reaction	Time for Fall of Systolic Pressure, Min.	Average Pulse Rate before Injection	Average Pulse Rate at Height of Reaction†	Pulse Rate at the Conclusion of Reaction
W. S.	108	120	32	56	54	35	71	82	74
J. F.	127	144	36	76	70	15	77	94	86
J. B.	121	138	32	73	60	34	78	86	76
R. W.	104	120	35	69	60	98	62	76	70
J. F.	113	120	18	74	80	10	81	82	76
M. F.	130	138	43	98	100	42	88	100	84
A. M.	88	106	10	49	55	80	72	92	74
F. S.	125	138	33	81	70	30	68	80	72
W. T.	103	113	44	51	60	32	69	86	76
D. C.	119	130	23	73	70	78	73	70	76
W. H.	94	110	40	62	64	30	66	80	72
S. D.	107	126	13	74	96	65	72	98	72
Average	110	125	30	70	70	45	73	86	76

\* Obtained by averaging all the readings taken before the injection (average of six readings for each case).

† Nearest reading to the systolic height, sometimes three minutes before the blood pressure height, sometimes three minutes later.

#### EFFECT OF EPINEPHRIN ON THE ELECTROCARDIOGRAM OF EPINEPHRIN-SENSITIVE INDIVIDUALS

The method used in these cases was as follows: First the patient was put to bed and kept quiet until the blood pressure became constant. When several readings at ten minute intervals showed a constant blood-pressure level, an electrocardiogram was taken. These were begun,

on an average, about forty-five minutes after the patients were put to bed. This electrocardiogram was adopted as a normal for the individual case.

Seven and a half minims of a 1:1,000 solution of epinephrin chlorid (freshly prepared from Parke, Davis & Co.'s adrenalin chlorid tablets) was then injected intramuscularly at the base of the deltoid. Bloodpressure readings were then taken every three minutes until the height of the rise was determined after which they were taken every ten minutes until it again reached normal. A second electrocardiogram was taken at the height of the response to epinephrin, and a third one

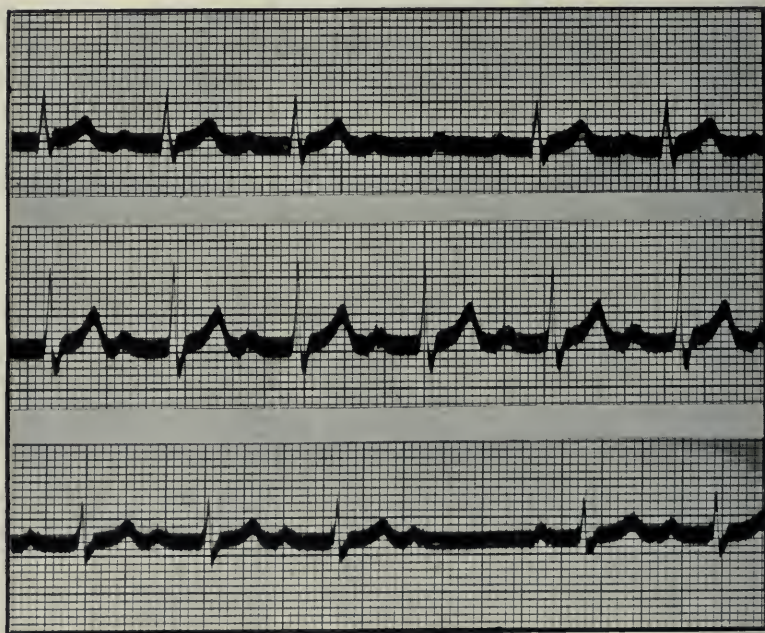


Fig. 1.—“Irritable heart” case. Record taken one and three-quarters hours after epinephrin injection. Lead I, P-R time 0.24 second; Lead II, P-R time 0.28 second; Lead III, P-R time 0.28 second. Blocked P-wave.

was taken at the time when the reaction was completed as shown by a return of the systolic pressure to the original level and a fall of the pulse to its level.

From Table 1 it appears that the characteristic reaction after the injection of epinephrin was a rise of the systolic blood pressure (the diastolic pressure remaining unchanged) and an increase in pulse rate. The reaction came on, on an average of thirty minutes after the injection, was manifested by an average increase of 15 mm. in the systolic

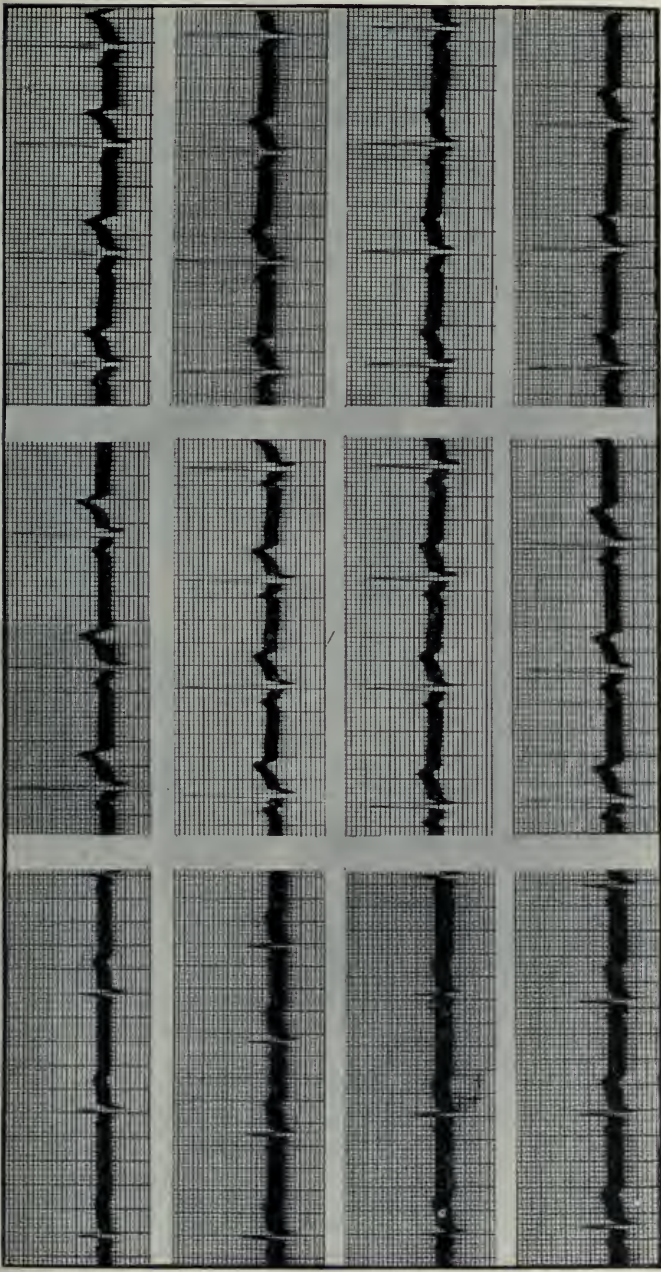


Fig. 2.—Effect of adrenalin on the normal electrocardiogram.

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
I. Before epinephrin injection (after 45 min. rest)....	57	0.16	0.34	1.00	60	0.16	0.36	4.00	65	0.18	0.34	4.00
II. 30 minutes after epinephrin injection.....	65	0.16	0.36	1.00	60	0.16	0.36	2.50	60	0.16	0.36	2.00
III. 1 hr. 15 min. after injection.....	57	0.16	0.36	1.00	62	0.16	0.36	2.00	62	0.16	0.36	1.50
IV. 24 hrs. after 1 (after 45 min. rest).....	68	0.16	0.34	1.50	60	0.16	0.36	3.00	62	0.16	0.34	2.50

pressure and an increased pulse rate (13 beats) and subsided in forty-five minutes.

After the completion of the blood pressure and pulse observations each patient was asked a series of questions: First, the symptoms which had originally caused him to report to the infirmary and their duration; second, the symptoms which he experienced after the injection, and third, whether he had ever had any similar symptoms before. In trying to interpret the results of this quizzing we had impressed on us con-

TABLE 2.—"IRRITABLE HEART" CASES. BEFORE EPINEPHRIN

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
W. S.	68	0.12	0.32	2.00	68	0.14	0.32	3.50	73	0.14	0.32	1.50
J. F.	88	0.14	0.30	2.50	91	0.14	0.30	4.00	83	0.14	0.32	1.50
J. B.	91	0.12	0.28	1.00	81	0.14	0.32	2.00	88	0.14?	0.32	1.50
R. W.	62	0.14	0.36	4.50	55*	0.18	0.36	6.00	57*	0.18	0.38	1.50
J. F.	79	0.14	0.30	4.00	70	0.16	0.30	3.50	76	0.16	0.34	1.00§
M. F.	94	0.12?	0.28	3.00	94	0.12	0.32	5.50	94	0.14	0.30	2.50
A. M.	94	0.14	0.30	3.50	80	0.16	0.32	4.00	88	0.16	0.34	1.50—
F. S.	65	0.14	0.34	2.50	70	0.14	0.36	3.00	71	0.14	0.36?	0.00
W. T.	68*	0.12	0.32	3.50	53	0.14	0.34	5.50	71	0.14	0.34	2.50
D. C.	76†	0.16	0.34	2.00	74‡	0.16	0.34	2.50	74‡	0.18	0.34	1.00
W. H.	72	0.16	0.36	2.00	65	0.18	0.36	6.00	74	0.16	0.36	2.50
S. D.	80	0.12	0.30	2.00	88	0.16	0.32	3.50	80	0.16	0.30	2.00
Aver.	77	0.13	0.31	2.70	74	0.15	0.33	4.08	77	0.15	0.33	1.75

\* Marked sinus arrhythmia. † Frequent ventricular extrasystoles. § Diphasic T-wave.

TABLE 3.—"IRRITABLE HEART" CASES. HEIGHT OF EPINEPHRIN REACTION

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
W. S.	76	0.12	0.32	1.50	76	0.14	0.34	1.50	76	0.12	0.36	0.50
J. F.	85	0.14	0.34	3.00	79	0.14	0.36	3.50	80	0.14	0.34	1.00
J. B.	74	0.14	0.34	1.00	73*	0.14	0.36	2.00	79	0.14	0.34	1.50
R. W.	70	0.16	0.36	3.00	71*	0.16	0.36	4.00	68	0.16?	0.36	1.50
J. F.	74*†	0.14	0.34	3.00	74*	0.16	0.32	3.50	68‡	0.16	0.32	1.50
M. F.	96	0.12	0.30	3.00	90	0.14	0.32	4.50	85	0.12	0.32	1.50
A. M.	66*	0.16	0.36	2.00	74*	0.16	0.36	2.50	68	0.16	0.36	0.50
F. S.	76	0.14?	0.34	1.00	74	0.14	0.36	1.50	71‡	0.12?	T-3 absent	
W. T.	85	0.14	0.32	2.00	80	0.16	0.32	2.50	85	0.16	0.32	1.00
D. C.	88‡	0.16	0.36	1.00	79‡	0.16	0.36	2.00	77	0.18	0.32	1.00
W. H.	71	0.16	0.36	1.50	68	0.16	0.36	2.50	68‡	0.16	0.36	1.00
S. D.	100	0.12?	0.28	1.00	100	0.16	0.32	2.00	100	0.14	0.32	1.00
Aver.	80	0.14	0.33	1.91	78	0.15	0.34	2.66	77	0.14	0.38	1.09

\* Marked sinus arrhythmia. † Frequent ventricular extrasystoles. ‡ Notched R-wave.

stantly the fact that we were dealing with varying degrees of intelligence and introspection in these patients. The following symptoms were noted in the histories of the twelve patients studied: Dizziness (11 cases); dyspnea (9 cases); precordial pain (8 cases); fainting (4 cases); palpitation (2 cases); "weak spells" (2 cases); irregularity of the heart (2 cases). After the injection of epinephrin, tremor was observed in ten cases; increased pulsation of the vessels of the neck in seven cases; flushing or pallor in four cases; increased warmth of

the skin in two cases; restlessness and sweating of the hands in one case each. One patient complained voluntarily of precordial pain. On subsequent questioning it appeared that dizziness was experienced by six patients; precordial pain by five patients; blurred vision by four patients; palpitation by four patients; headache by two patients; irregularity of the heart, pressure in arms and legs, weakness, tremor and excitement, each by one patient.

#### SYMPTOMS AFTER EPINEPHRIN INJECTION

Separate records were kept of the symptoms which were actually observed after the injection of epinephrin, of those volunteered by the

TABLE 4.—“IRRITABLE HEART” CASES. CONCLUSION OF EPINEPHRIN REACTION

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
W. S.	69	0.12	0.32	2.00	66	0.14	0.36	3.00	66	0.14	0.36	1.50
J. F.	66	0.16	0.36	2.50	71	0.14	0.36	3.50	66*†	0.14?	0.36	1.00
J. B.	65	0.12	0.36	1.00	66*	0.14?	0.36	3.50	65	0.14?	0.36	2.50
R. W.	66*	0.16	0.36	3.50	70*	0.16	0.36	4.50	70	0.16	0.36	1.50
J. F.	76	0.16?	0.34	3.00	71	0.16	0.34	4.00	79†	0.16	0.36	2.00
M. F.	83	0.14?	0.32	3.00	80	0.16	0.30	5.50	80	0.14	0.34	2.00
A. M.	68	0.16	0.36	3.00	79	0.16	0.36	3.50	63	0.16	0.32	1.00—
F. S.	62	0.14	0.40	2.50	65	0.14	0.38	2.00	65	0.14?	0.36	0.50—
W. T.	81*	0.16	0.36	2.50	76	0.16	0.34	3.00	71	0.16	0.32	2.00
D. C.	81†	0.16	0.36	1.00	81*†	0.18	0.36	2.00	70*†	0.18	0.36	1.00
W. H.	70*	0.16	0.36	1.50	70*	0.18	0.36	3.00	73	0.18	0.36	1.50
S. D.‡												
Aver.	71	0.14	0.35	2.36	72	0.15	0.35	3.40	69	0.15	0.35	1.66

\* Marked sinus arrhythmia. † Frequent ventricular extrasystoles. ‡ Notched R-wave.

# Record not obtained.

TABLE 5.—EPINEPHRIN SENSITIVE “IRRITABLE HEART” CASES

	Before Injection			At Height of Reaction			At the End of Reaction		
	I	II	III	I	II	III	I	II	III
Rate.....	77	74	77	80	78	77	71	72	69
P-R time (second).....	0.13	0.15	0.15	0.14	0.15	0.14	0.14	0.15	0.15
R-T time (second).....	0.31	0.33	0.33	0.33	0.34	0.33	0.35	0.35	0.35
T-wave (mm.).....	2.70	4.08	1.75	1.91	2.66	1.09	2.36	3.40	1.66

patient, and of those which could be brought out by questioning. Ten of the patients stated that the symptoms which they experienced after the injection of epinephrin were the same in nature as those which they had had many times before and for which they had sought medical aid. Two of the patients could make no association between their symptoms and previous experiences. One of the patients said that the attack was more severe than any which he had had before (this patient had ventricular extrasystoles which were increased in number by the epinephrin). Another of the patients complained of a “jarring

sensation" which he had never had before. (The tracing of this patient after epinephrin showed ventricular extrasystoles.)

It will be of interest to compare the three sets of electrocardiograms in these cases: the normals taken when the patients had been quiet in bed for over thirty minutes, when the blood pressure and pulse rate were constant; those taken at the height of the epinephrin reaction when the systolic pressure and pulse rate were elevated and the patients were experiencing their typical symptoms; and finally the records taken at the conclusion of the reaction.

TABLE 6.—NORMAL CASES. BLOOD PRESSURE AND PULSE CHART

Initials	Normal Systolic Pressure*	Systolic Pressure at Height, 30 Min. after Injection†	Normal Diastolic Pressure*	Diastolic Pressure at Height, 30 Min. after Injection†	Pulse Rate before Injection	Pulse Rate at Height of Reaction	Pulse Rate at the Conclusion
F. E.	120	120	70	70	74	80	76
H. B.	110	114	80	80	84	72	72
W. J.	100	98	60	60	70	72	72
L. H.	115	120	65	65	73	80	72
G. B.	119	120	80	80	74	76	76
F. B.	116	114	68	66	70	68	68
W. W.	125	120	70	70	65	64	64
E. C.	116	116	70	70	64	76	72
J. D.	107	118	71	70	75	88	84
T. O'C.	97	98	64	60	60	64	68
A. S.	115	114	70	70	72	72	72
A. O.	103	100	60	60	82	84	76
Average	111	112	69	69	71	74	72

\* Obtained by averaging all the readings taken before the injection.

† These readings were made about 30 minutes after the injection of epinephrin.

TABLE 7.—NORMALS. BEFORE EPINEPHRIN

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
F. E.	68	0.16	0.36	5.00	68	0.14	0.36	3.50	70	0.14	0.32	1.00§
H. B.	81	0.14	0.32	3.50	76	0.16	0.32	4.00	78	0.18	0.34	1.00
W. J.	67*	0.16	0.36	2.00	66*	0.16	0.36	5.00	66*	0.16?	0.36	3.50
L. H.	68†	0.16	0.32	3.00	74†	0.14	0.34	3.00	79*	0.14	0.34¶	1.00§
G. B.	70*	0.20	0.34	5.00	68	0.20	0.36	5.00	75	0.16?	0.36	1.00
F. B.	64*	0.12	0.36	1.50	61*	0.16	0.34	4.00	70*	0.16	0.34	3.00
W. W.	68*	0.12	0.36	2.50	68*	0.12	0.36	7.00	58	0.14	0.36	4.50
E. C.	56†	0.20	0.40	2.00	61*	0.24	0.40	3.00	61†	0.24	0.40	0.50
J. D.	78†	0.16	0.32	2.00	83†	0.16	0.32	3.50	78*	0.18	0.34	2.00
T. O'C.	60	0.14	0.40	3.00	57	0.16	0.38	4.00	62	0.16	0.38	1.00
A. S.	83	0.16	0.34	3.00	71	0.16	0.34	5.00	77*	0.16	0.34	2.00
A. O.	80	0.16	0.34	1.50	83	0.16	0.32	1.50	83	0.16	0.32	0.50§
Aver.	70	0.15	0.35	2.83	69	0.16	0.35	4.04	71	0.16	0.35	1.75

\* Marked sinus arrhythmia.

† Very marked sinus arrhythmia.

§ Diphasic T-wave.

¶ Notched R-wave.

#### METHODS OF MEASUREMENT OF THE ELECTROCARDIOGRAMS

*Rate.*—The mean rate for each lead was calculated by determining the maximal and the minimal rates in the lead and averaging the results. In all cases in which there was a variation of 0.12 of a second

or more between beats it was considered that sinus arrhythmia was marked in the lead. A variation of from 0.16 to 0.24 of a second was considered to indicate very marked sinus arrhythmia.

*R-T Time.*—This was determined by measuring the time interval between the Q-wave and the end of the T-wave. It was possible to measure this to within a half millimeter error.

TABLE 8.—NORMALS. HEIGHT OF EPINEPHRIN REACTION

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
F. E.	83	0.16	0.34	3.00	98	0.16	0.36	1.50	98	0.16	0.32†	0.50§
H. B.	75	0.16	0.36	2.50	75	0.16	0.36	3.50	78	0.18	0.32	1.00
W. J.	62	0.16	0.38	1.50	73*	0.16?	0.40	3.50	67†	0.16?	0.36	2.50
L. H.	82†	0.16	0.34	2.00	83*	0.16	0.34	2.00	81*	0.16	0.32†	0.50§
G. B.	78	0.18	0.36	3.00	78	0.20	0.34	3.00	83	0.18	0.34†	1.00—
F. B.	66*	0.12	0.36	1.00	70*	0.14	0.36	1.50	68*	0.16	0.36	1.00
W. W.	60	0.12	0.36	1.00	60	0.14	0.40	5.00	60	0.14	0.36	4.00
E. O.	65	0.20	0.42	1.50	70*	0.24	0.40	1.50	71†	0.22	0.40	0.50
J. D.	85*	0.16	0.34	1.50	85	0.16	0.34	3.00	83	0.16	0.34	1.50
T. O' C.	64*	0.14	0.40	2.50	65	0.16	0.38	2.50	65	0.16	0.38	1.50
A. S.	75	0.14	0.36	2.00	75*	0.16	0.36	3.50	71	0.16	0.36	1.50
A. O.	78	0.14	0.36	1.50	77*	0.16	0.34	1.00	78	0.16	0.34?	0.50
Aver.	72	0.15	0.36	1.91	75	0.16	0.36	2.62	74	0.16	0.35	1.36

\* Marked sinus arrhythmia.

† Very marked sinus arrhythmia.

§ Diphasic T-wave.

† Notched R-wave.

TABLE 9.—NORMALS. CONCLUSION OF EPINEPHRIN

	Lead I				Lead II				Lead III			
	Rate	P-R	R-T	T	Rate	P-R	R-T	T	Rate	P-R	R-T	T
F. E.	77*	0.16	0.36	3.00	77*	0.16	0.36	2.50	88	0.16	0.32	1.00—
H. B.	71	0.16	0.36	3.00	68	0.16	0.36	3.50	68	0.16?	0.36	1.00
W. J.	58*	0.16	0.36	1.50	65	0.16	0.40	6.00	62	0.16	0.40	4.00
L. H.	69†	0.14	0.36	2.00	67†	0.14	0.36	1.00	71*	0.16	0.34†	1.00
G. B.	71	0.20	0.36	4.50	78	0.20	0.36	3.50	71*	0.16	0.32†	1.00—
F. B.	72†	0.14	0.36	1.00	64*	0.16	0.36	2.00	70†	0.16	0.36	1.00
W. W.	62	0.14	0.36	2.00	62	0.14	0.36	5.00	57	0.14	0.36	4.00
E. O.	66*	0.24	0.40	2.00	62	0.24	0.40	3.00	64*	0.24	0.40	1.00
J. D.	74*	0.16	0.34	1.50	78	0.16	0.34	3.00	88	0.16	0.34	2.00
T. O' C.	65†	0.14	0.38	3.00	65	0.16	0.40	3.00	62	0.16	0.38	1.00
A. S.	65	0.16	0.36	3.00	68	0.16	0.36	4.50	73*	0.16	0.36	2.00
A. O.	75	0.16	0.34	1.50	75	0.16	0.36	1.50	75	0.16	0.36?	0.50—
Aver.	68	0.16	0.36	2.33	69	0.16	0.36	3.20	70	0.16	0.35	1.88

\* Marked sinus arrhythmia.

† Very marked sinus arrhythmia.

§ Diphasic T-wave.

† Notched R-wave.

All measurements were made under a reading glass, and it is believed that careful measurements by this method involved an experimental error of not more than half a millimeter, which is believed to be the best that can be done. Measuring under magnification certainly reduced the error a great deal. The various tables of measurements were made consecutively, i. e., all the "normals" were measured first, then the records at the "height of the epinephrin reaction," and finally the records at the "conclusion." This was done in order to avoid all possibility of prejudice in measuring the records.

The galvanometer fiber used in these studies was made of glass quartz covered with a gold plate. Lieut. F. W. Keyes, S. C., U. S. Army, maker of the fiber, gives the following data: Length of fiber 13.5 cm.; diameter of fiber, 3.00 microns; resistance, 4,620 ohms; deflection time, 0.02 of a second. The galvanometer was designed by Capt. Horatio B. Williams, Eng. Corps, U. S. Army, for research purposes.

TABLE 10.—SUMMARY OF NORMAL CASES

	Before Injection			30 Minutes after Injection			75 Minutes after Injection		
	I	II	III	I	II	III	I	II	III
Rate.....	70	69	71	72	75	74	68	69	70
P-R time (second).....	0.15	0.16	0.16	0.15	0.16	0.16	0.16	0.16	0.16
R-T time (second).....	0.35	0.35	0.35	0.36	0.36	0.35	0.36	0.36	0.35
T-wave (mm.).....	2.83	4.04	1.75	1.91	2.62	1.36	2.33	3.20	1.88

In the twelve cases hypersensitive to epinephrin, which were the subject of careful electrocardiographic study, many of the gross irregularities noted incidentally in the first group of eight cases, did not occur. Thus no changes were noted in the conduction time. Inasmuch as control records were obtained before the injection and after the reaction was completed, as well as at the height of the reaction, a basis was obtained for observing any effect on the length of systole and the height of the T-wave. The length of systole, as represented by the R-T time of the electrocardiogram, was not affected by the injection of epinephrin. In lead I the average height of the T-wave before the injection was 2.70 mm. This dropped to 1.91 mm. at the height of the reaction, and rose to 2.36 mm. at the end. In lead II the average height of the T-wave before injection was 4.08 mm., 2.66 mm. at the height of the reaction, and 3.40 at the end of the reaction. In lead III the average height of the T-wave was 1.75 mm. before the injection, falling to 1.09 mm. at the height of the reaction and measuring 1.66 mm. at the end.

There is, then, a slight but perfectly definite decrease in the height of the T-wave at the height of the epinephrin reaction. This is seen, in the averages, in all three leads. Apparently, this change is of relatively short duration, since the records taken at the conclusion of the reaction show the T-wave gradually increasing to the height found before the injection was made. Electrocardiograms were taken of several cases the day after the injection and in all the T-wave was found to have increased to its former height.

It had at first seemed possible that the symptoms complained of by the patients at the height of the epinephrin reaction might be due to changes in the action of the heart. The evidence of the electrocardiogram does not, however, confirm this suggestion. Some of the patients noted symptoms during the reaction while others did not, and the effect on the electrocardiogram was usually very slight and practically the same in all cases.

TABLE 11.—COMPARATIVE TABLE OF HEIGHT OF T-WAVES OF "IRRITABLE HEART" AND NORMAL CASES

	Lead I				Lead II				Lead III			
	Irritable Heart	Decrease	Normal Cases	Decrease	Irritable Heart	Decrease	Normal Cases	Decrease	Irritable Heart	Decrease	Normal Cases	Decrease
A	2.70	....	2.83	....	4.08	....	4.04	....	1.75	....	1.75	....
B	1.91	0.79	1.91	0.92	2.66	1.42	2.62	1.42	1.09	0.66	1.36	0.39
C	2.36	0.34	2.33	0.50	3.40	0.68	3.20	0.84	1.66	0.09	1.88	+0.13

A. Before injection of epinephrin.

B. At height of epinephrin reaction (30 minutes after the injection, in the case of normals).

C. At conclusion of epinephrin reaction (75 minutes after the injection, in the case of normals).

#### NORMAL CASES

Following the studies made on cases of "irritable heart," a series of twelve normal men was studied. These men were all overseas men who had been under fire. They came from the surgical service; they were all ambulatory and had been sent to this hospital for convalescence. Their wounds were all healed and none had had any cardiac trouble or had shown the symptoms of "effort syndrome."

#### EFFECT OF EPINEPHRIN ON THE ELECTROCARDIOGRAM OF NORMAL CASES

The methods used in studying these cases were the same as those used in studying the "irritable heart" cases. The second electrocardiogram, representing the effect produced at the height of the epinephrin reaction, was taken about thirty minutes after the injection. This time interval was found to represent the average time for the height of the reaction in the "irritable heart" cases. The final electrocardiogram was taken forty-five minutes after the second record, which was found to be the average time required for the reaction to pass off completely in the "irritable heart" cases. During this interval between the second and the third electrocardiograms of normal cases blood pressure and pulse observations made at ten minute intervals showed no delayed rise in the normal cases.

From Table 6 it appears that epinephrin has slight effect on either systolic blood pressure or pulse rate in normal men. Similarly, no pronounced subjective symptoms were produced in this group, in contrast to the results in cases of "irritable heart."

Table 11 shows a comparison of the height of the T-wave in normals and in cases of "irritable heart" before the injection, at the height of the reaction, and at the conclusion of the reaction. No appreciable difference exists between the two types of cases, in fact, in a number of instances, the figures are practically identical. It is thus interesting that in the normal subject there is a complete absence of symptoms which are characteristically produced by the injection of epinephrin in patients with "irritable heart."

#### CONCLUSIONS

1. The effect of epinephrin has been observed in normal individuals and in a number of patients with the symptoms of "irritable heart." All of the latter were hypersensitive to epinephrin in the sense that they gave a much more pronounced reaction to a small dose of the drug than do normal individuals.

2. In some cases gross abnormalities of the electrocardiographic record were observed. The following were the most important deviations from the normal: Changes in conduction (delayed conduction, partial heart block) and the production of ventricular extrasystoles.

3. Special studies were made of the effect of epinephrin on the conduction time, length of systole and height of the T-wave in twelve epinephrin hypersensitive patients with "irritable heart" and in twelve normal men. No changes were found in the conduction time or the length of systole in either type. In both at the height of the reaction there was a decrease in the height of the T-wave.

4. An attempt has been made to correlate the symptoms complained of by the patients with "irritable heart" at the height of the reaction with abnormalities of the electrocardiogram, but no definite association could be made.

It is a great pleasure for me to express my indebtedness to the medical and the surgical staffs of General Hospital No. 9 for interest and cooperation in these investigations. The chiefs of the cardiovascular division, Major Francis W. Peabody and Capt. Bertnard Smith, M. C., U. S. Army, have carefully supervised the work of this laboratory. I am particularly indebted to Lieut. Joseph T. Wearn, M. C., U. S. Army, and Miss Edna H. Tompkins, whose epinephrin studies on "irritable heart" cases stimulated me to undertake these investigations. My laboratory assistants, Lieut. Frederick W. Keyes, S. C., and Serg. Thomas H. Ford, Medical Department, U. S. Army, have given invaluable assistance in the technical work involved in these studies.

# AN EXPERIMENTAL ENDOTHELIAL LEUKOCYTOSIS IN GUINEA-PIGS \*

## FIFTH REPORT OF STUDIES ON THE MONONUCLEAR LEUKOCYTES OF THE BLOOD

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In laboratory animals there may be produced a neutrophilic leukocytosis by infectious agents such as the pyogenic cocci, or by chemical substances such as croton oil. A less striking increase of the eosinophils has been produced by extracts of certain parasitic worms. Aside from the diagnostic significance of variations in the number of leukocytes in human blood, there are indications that the reaction of cells present there is a factor in the resistance to the infection. The development of a method<sup>1</sup> for the identification of endothelial leukocytes made it possible not only to determine the percentage of these cells present normally in the blood of experimental animals, but also to test the effect on the endothelial leukocyte count of bacterial and animal proteins and of chemical compounds. The guinea-pig was chosen for the experiments largely on account of its freedom from natural infections of a chronic nature.

Blood is best obtained from the guinea-pig by snipping with scissors to the distance of 2 or 3 mm. the margin of the shaved and perfectly dry ear, and expressing small drops of blood by compressing and making slight lateral pressure. The covers are touched to the top of the small drops. No less than two dozen smears are made, and four of these are stained by the granular leukocyte stain<sup>1</sup> for the percentage count of leukocytes present. The blood pipet for the enumeration of the white cells is filled at the same time, in order that the total number of the various leukocytes may be determined from the differential counts. The percentage of endothelial leukocytes in normal guinea-pig blood is subject to considerable variation just as it is in human blood. In fifteen animals (Nos. 10, 12, 33, 35, 67, 68, 69, 70, 71, 76, 79, 80, 82, 83 and 86) this varied between 0.5 and 3.1 per cent., with an average of 1.58 per cent.

Synthetic dyes were made the subject of investigation on account of the known property of certain ones to enter the cytoplasm of endothelial cells and leukocytes when introduced as in intravital

\* From the Department of Pathology, Marquette Medical School.

1. McJunkin, F. A., and Charlton, Alice G.: Arch. Int. Med. **22**:157 (Aug.) 1918.

## RESULTS OF EXPERIMENTAL STUDY ON LEUKOCYTES

Number	Date	Weight	Dosage	Leukocytes per C.Mm.	Differential Count*
10	May 9	840	.....	.....	350 cells counted; percentages: L, 64.7; N, 25.6; E, 6.8; B, 0.5; End, 2.4
	May 14	...	1 c.c. heavy suspension <i>B. subtilis</i> intraperitoneally (i. p.)		
	May 15	...	Same as May 14		
	May 17	...	.....	.....	1,430 cells counted; percentages: L, 39.6; N, 50.5; E, 8.4; B, 0.5; End, 1.0
	May 21 (killed)	...	.....	.....	792 cells counted; percentages: L, 48; N, 46.6; E, 2.5; B, 0.6; End, 2.3
12	Nov. 1	385	.....	16,000	595 cells counted; percentages: L, 55.5; N, 42.7; E, 0.3; B, 0; End, 1.5
	Nov. 4	...	.....	14,500	No differential count
	Nov. 5	...	½ slant, <i>B. typhosus</i> i. p.		
	Nov. 7	...	Same as Nov. 5	12,500	1,346 cells counted; percentages: L, 47.6; N, 49.5; E, 0.5; B, 0; End, 2.4
	Nov. 8	...	.....		
	Nov. 12	...	1 slant		
	Nov. 13 (killed)	...	.....	23,000	1,756 cells counted; percentages: L, 23.5; N, 73.2; E, 0.5; B, 0.5; End, 2.3
13	Dec. 4	417	Suspension entire lungs of normal guinea-pig (ground in mortar) i. p.		
	Dec. 9	...	Same as Dec. 4		
	Dec. 11	...	Same as Dec. 4		
	Dec. 16 (killed)	...	.....	19,000	582 cells counted; percentages: L, 36; N, 58.6; E, 2.7; B, 1.0; End, 1.7
17	Jan. 9	650	5 c.c. heavy suspension beef lung (ground in mortar) i. p.		
	Jan. 17 (killed)	675	.....	20,000	968 cells counted; percentages: L, 56.5; N, 25; E, 14.1; B, 1.4; End, 3.0
19	Jan. 9	660	5 c.c. same suspension as No. 17		
	Jan. 13	...	Same as Jan. 9		
	Jan. 17	...	Same as Jan. 9		
	Jan. 22 (killed)	...	.....	.....	860 cells counted; percentages: L, 53.5; N, 27; E, 13; B, 5; End, 1.5
33	Feb. 20	640	.....	11,000	440 cells counted; percentages: L, 39.8; N, 38.7; E, 18.2; B, 1.1; End, 2.2
	Feb. 27	...	10 c.c. of 2 per cent. (approximate) suspension sudan III in 1 per cent. gelatin; i. p.		
	Feb. 28	...	20 c.c.		
	March 3	...	10 c.c.		
	March 4 (dead)	...	10 c.c. ....	17,000	635 cells counted; percentages: L, 33; N, 62; E, 0.9; B, 0; End, 4.1

\* L, lymphocytes; N, neutrophils; E, eosinophils; B, basophils; End, endothelial leukocytes.

## RESULTS OF EXPERIMENTAL STUDY ON LEUKOCYTES—(Continued)

Number	Date	Weight	Dosage	Leukocytes per C.Mm.	Differential Count*
35	March 5	520	28 mg. arsphenamin; i. p.	12,200	1,318 cells counted; percentages: L, 26.9; N, 68.8; E, 0.3; B, 0.9; End, 3.1
	March 10	...	40 mg. arsphenamin; i. p.		
	March 13 (killed)	...	.....	7,500	792 cells counted; percentages: L, 50.2; N, 34.8; E, 9.5; B, 2.5; End, 3
43	March 12	190	1 c.c. suspension tubercle bacilli (about 8,000 bacilli) of the human type i. p.		
	March 19	215			
	March 26	220			
	March 29	200	.....	35,200 (includes nucleated red cells)	941 cells counted; percentages: L, 17.9; N, 75.2; E, 0.2; B, 0; End, 6.7; numerous nucleated red cells
	April 2	185	.....		Percentages: L, 35; N, 53.5; E, 0.6; B, 1.6; End, 9.3; numerous nucleated red cells
44	April 9 (dead)				
	March 12	385	1 c.c. suspension tubercle bacilli (see No. 43)		
	March 26	245	.....	22,400	1,310 cells counted; percentages: L, 17.7; N, 70.6; E, 0.6; B, 0; End, 11.1; numerous nucleated red cells
60	March 30 (dead)				
	April 4	215	1 c.c. suspension tubercle bacilli human type (about 1 bacillus per oil immersion field i. p.)		
	May 26 (killed)	...	.....	7,000	818 cells counted; percentages: L, 40.8; N, 47.6; E, 0.3; B, 1.8; End, 9.5; 94 erythroblasts
62	April 4	385	1 c.c. suspension tubercle bacilli (see No. 60)		
	May 27	190	.....		836 cells counted; percentages: L, 63.9; N, 18.9; E, 0.3; B, 0.6; End, 16.3
	May 28 (dead)				
64	April 4	262	1 c.c. suspension tubercle bacilli (see No. 60)		
	May 16	...	.....	21,900	1,500 cells counted; percentages: L, 22.4; N, 68.3; E, 0.2; B, 0.1; End, 9
	May 26 (killed)	285	.....	36,000	1,610 cells counted; percentages: L, 30.3; N, 60.5; E, 0.2; B, 0.3; End, 8.7; 50 erythroblasts
65	April 4	202	1 c.c. suspension tubercle bacilli (see No. 60)		
	May 20	225	.....	15,500	1,410 cells counted; percentages: L, 42.6; N, 47.2; E, 0.5; B, 0.3; End, 9.4
	May 30 (killed)				

\* L, lymphocytes; N, neutrophils; E, eosinophils; B, basophils; End, endothelial leukocytes.

## RESULTS OF EXPERIMENTAL STUDY ON LEUKOCYTES—(Continued)

Number	Date	Weight	Dosage	Leukocytes per C.Mm.	Differential Count*
67	April 22	635	.....	15,500	942 cells counted; percentages: L, 59.4; N, 31.4; E, 7.4; B, 0.5; End, 1.3
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, i. p.		
	May 2	640	5 c.c. ....	21,000	1,034 cells counted; percentages: L, 32; N, 59; E, 4.8; B, 0.5; End, 3.7
	May 9	...	5 c.c. ....	20,200	1,248 cells counted; percentages: L, 34.3; N, 57.5; E, 4.8; B, 0.2; End, 3.2
	May 14 (dead)				
68	April 22	490	.....	13,800	1,120 cells counted; percentages: L, 53.8; N, 40.4; E, 4.3; B, 0.3; End, 1.2
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, i. p.		
	May 2	465	.....	16,100	970 cells counted; percentages: L, 38.1; N, 54.5; E, 0.6; B, 0.4; End, 6.4
	May 9	485	.....	15,800	1,186 cells counted; percentages: L, 21.5; N, 70; E, 3.6; B, 0; End, 4.9; many nucleated red cells
	May 13 (dead)				
69	April 22	375	.....	12,200	975 cells counted; percentages: L, 58.8; N, 33.8; E, 5.6; B, 0.4; End, 1.4
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, i. p.		
	May 1	...	.....	14,200	1,140 cells counted; percentages: L, 33.6; N, 59.3; E, 3; B, 0; End, 4.1
	May 2 May 8	380 390	.....	12,800	610 cells counted; percentages: L, 39.8; N, 51.6; E, 4.2; B, 0; End, 4.4; few nucleated red cells
	May 9 May 14 (killed)	... 398	4 c.c. .....	10,900	500 cells counted; percentages: L, 28; N, 62; E, 5.4; B, 0; End, 4.6; many nucleated red cells
70	April 22	437	.....		
	April 23	...	.....	17,000	1,210 cells counted; percentages: L, 46.2; N, 47.8; E, 3.3; B, 0.6; End, 2.1
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, subcutaneously		
	April 30	435	.....	19,500	1,096 cells counted; percentages: L, 31.9; N, 60; E, 3.8; B, 0.8; End, 3.5
	May 2 May 7	440 405	5 c.c. .....	18,800	1,046 cells counted; percentages: L, 28.5; N, 62.7; E, 4.8; B, 0.2; End, 3.8; a few nucleated red cells
	May 9 May 14 (killed)	... 365	4 c.c. .....	24,400	1,166 cells counted; percentages: L, 28.3; N, 66.1; E, 2.4; B, 0; End, 3.2; a few nucleated red cells

\* L, lymphocytes; N, neutrophils; E, eosinophils; B, basophils; End, endothelial leukocytes.

RESULTS OF EXPERIMENTAL STUDY ON LEUKOCYTES—(Continued)

Number	Date	Weight	Dosage	Leukocytes per C.Mm.	Differential Count*
71	April 22	515	.....	17,000	1,048 cells counted; percentages: L, 37; N, 45.8; E, 13.6; B, 0.8; End, 2.8
	April 25	...	5 c.c. of 2 per cent. sudan III in olive oil, subcutaneously		
	April 29	480	.....	14,200	1,138 cells counted; percentages: L, 13.5; N, 81.4; E, 0.3; B, 0; End, 4.8
	May 2	475	5 c.c.		
	May 6	...	.....	18,600	1,150 cells counted; percentages: L, 30.4; N, 60.5; E, 4; B, 0.3; End, 4.8
	May 9 May 13 (killed)	...	4 c.c. .....	18,400	1,272 cells counted; percentages: L, 33.1; N, 60.8; E, 2.9; B, 0; End, 3.2; 2 nucleated red cells
76	May 16	305	10 c.c. of colloidal solution of sudan III (about 0.5 per cent.) i. p.	8,200	890 cells counted; percentages: L, 52.2; N, 44.2; E, 1.6; B, 0.3; End, 1.7
	May 17	...	10 c.c.		
	May 19	...	10 c.c.		
	May 21 (killed)	285	.....	12,900	1,060 cells counted; percentages: L, 42.5; N, 52.5; E, 2.2; B, 0.3; End, 2.5
79	May 23	405	1 c.c. of 2 per cent. Bismarck brown, i. p.	8,400	415 cells counted; percentages: L, 61.8; N, 37.7; E, 0; B, 0; End, 0.5
	May 26	...	2 c.c.		
	May 27	...	4 c.c.		
	May 28 (killed)	...	.....	17,800	1,225 cells counted; percentages: L, 20.2; N, 78; E, 0.3; B, 0.2; End, 1.3
80	May 26	395	1 c.c. of 2 per cent. eosin, i. p.	8,600	776 cells counted; percentages: L, 61.4; N, 37; E, 0.5; B, 0.5; End, 0.6
	May 27	...	2 c.c.		
	May 28 (killed)	...	.....	7,000	766 cells counted; percentages: L, 63.9; N, 33; E, 0; B, 0.7; End, 2.4
82	June 2	395	0.5 c.c. of 0.25 per cent. crystal violet, i. p.	6,300	608 cells counted; percentages: L, 74; N, 17; E, 7.5; B, 0.5; End, 1
	June 7	415	1 c.c.		
	June 9 (killed)	420	.....	8,300	784 cells counted; percentages: L, 57.5; N, 34.7; E, 5.3; B, 1.2; End, 1.3
83	June 2	355	0.5 c.c. of 0.25 per cent. methylene blue, i. p.	.....	395 cells counted; percentages: L, 53.5; N, 38.5; E, 6.1; B, 0.7; End, 1.2
	June 9 (killed)	380	1 c.c. ....	7,500	631 cells counted; percentages: L, 53.2; N, 31.7; E, 12; B, 1; End, 2.1
86	June 3	360	0.5 c.c. of 0.1 per cent. night blue, i. p.	7,000	820 cells counted; percentages: L, 59.7; N, 39.2; E, 0.3; End, 0.8
	June 5 (killed) ++	...	.....	6,000	313 cells counted; percentages: L, 26.8; N, 72.3; E, 0; B, 0.3; End, 0.6

\* L, lymphocytes; N, neutrophils; E, eosinophils; B, basophils; End, endothelial leukocytes.

staining. Grüber's dyes were used in all instances. No increases in endothelial leukocytes were produced by Bismarck brown, eosin (yellowish, water soluble), crystal violet, methylene blue or night blue (Nos. 79, 80, 82, 83 and 86). Sudan III, in large doses, produces quite regularly an increase above the maximum of 3.1 per cent. (No. 35) met with in normal guinea-pigs, and this dye was administered in varying amounts and by different methods in an attempt to produce a marked endothelial leukocytosis extending over a considerable time without killing the animal. This was not successful. The highest count is seen in No. 68, one week after an intraperitoneal injection of the dye in solution in olive oil. The average of fourteen counts taken from Nos. 33, 67, 68, 69, 70, 71 and 76 is 4.1 per cent. In normal guinea-pigs usually more lymphocytes are present than neutrophils, but a few days after a large injection of sudan III the neutrophils are in excess. If the number of eosinophils is great in the untreated animal these are decreased by the action of the dye. A moderate anemia develops and nucleated red cells appear in the blood.

In guinea-pig blood, after staining with a polychrome blood stain, it is even more difficult to identify endothelial leukocytes than it is in human blood since a greater percentage of these cells approaches the lymphocytes in size and shape. With the alphanaphthol stain<sup>1</sup> the endothelial leukocytes have very distinct blue granules often clumped in the indented portion of the nucleus, and in the parts of smears properly spread they are readily identified. The neutrophils have blue granules less distinct than those of human blood and the cytoplasm is practically unstained. The eosinophilic granules appear as large refractive ringlike spherules with a bluish periphery. The large basophilic granules are a deep red or purple. So far as this stain is concerned, there is no basis for offering a classification for the leukocytes different from the one adopted for human blood. The reasons for regarding the mononuclear cell with blue cytoplasmic granules as of endothelial origin have been given fully in previous reports.

The liver, kidneys, adrenals, spleen, omentum, lungs and heart were fixed in Zenker's fluid and stained with eosin-methylene blue. The histologic changes are confined to the abdominal organs of the animals injected intraperitoneally. In the animals receiving aqueous suspensions of the dye, adhesions in the peritoneal cavity, especially about the liver, are marked and microscopically fibroblastic proliferation has taken place in the omentum; here endothelial leukocytes containing particles of the dye have accumulated. The fibrous capsule of the liver is thickened, and directly beneath it the liver cells about the periportal tissue have become necrotic. In No. 70 the necrotic

liver cells are being ingested by endothelial leukocytes. A few mitoses are present in the zona glomerulosa of the suprarenal cortex and scattered necrotic cells are found in the inner portion of the cortex.

The typhoid bacillus which produces an endothelial reaction regularly in human tissue, as shown by Mallory,<sup>2</sup> does not cause an endothelial leukocytosis in guinea-pigs (No. 12). Negative results followed injections of bacillus subtilis. A number of animals were given suspensions of organs made by grinding them up aseptically with sand in a mortar; others received autolysates of guinea-pig lungs, beef lungs and beef spleen. No marked or constant increases were observed (Nos. 13, 17, 19). Asphenamin, ox-bile and solutions of ether proved negative.

Although a moderate endothelial leukocytosis may be produced by intraperitoneal injections of sudan III in amounts that lead to the death of the animal in a few weeks, in no case was an increase to 10 per cent. noted. In the later stages of the tuberculosis in guinea-pigs induced in the usual way, the percentage found in the sudan III experiments is quite regularly exceeded, and the endothelial leukocytosis persists until the animal dies. In view of the small percentage of these cells present in normal guinea-pigs (1.5), the blood picture in tubercular animals, such as No. 62 with the leukocytes reaching 16.3 per cent., is a striking one. The increase may appear within two weeks from the time of inoculation (No. 44). In eight counts on six tubercular animals (Nos. 43, 44, 60, 62, 64 and 65) an average of 10 per cent. of endothelial leukocytes is present. At necropsy the tissues in the six animals present the usual picture with miliary and conglomerate tubercles in the liver and lungs, and caseous masses measuring one centimeter in the greatly enlarged spleen.

#### CONCLUSIONS

Although there are few endothelial leukocytes normally present in the peripheral blood as compared with the neutrophils or lymphocytes, the percentage may be increased regularly by experimental procedures. It appears after an examination of the usual textbooks and a cursory examination of the literature that a characteristic increase in number in human blood of this variety of leukocyte has not been noted in generalized miliary or other forms of tuberculosis. Such a leukocytosis is present in the later stages of the usual experimental tuberculosis of guinea-pigs.

2. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914.

## NECROPSY STUDIES AT A HOSPITAL CENTER \*

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### INTRODUCTION

The study in this paper covers a vast amount of material examined in a relatively short period of time. It is therefore more extensive than intensive. It is not possible to give an exhaustive discussion of all the lesions encountered—for that would involve little short of an unabridged treatise on pathology—but rather to give a brief and hurried résumé of all of the important pathologic conditions that came under observation. In the period under discussion, more than 30,000 patients passed through the center. At one time more than 20,000 patients and personnel were quartered here. The heavy pressure of work from all sides, together with the absence of proper library facilities, makes it impossible to give much more than a cursory sketch of the grosser details of the postmortem findings.

During the period included between July 23, 1918—when the first convoy of patients arrived at this center—and Jan. 1, 1919, there are recorded a total of 429 deaths. Of this number, about fifteen bodies were not necropsied for reasons other than the lack of time; these dead included nurses, officers from the personnel, allied soldiers, several bodies brought in crushed in railroad accidents, and one case of drowning among the enlisted personnel. The number of necropsies performed during this period was 356, or about 86 per cent. of the total possible number. This percentage is not inconsiderable when one observes the constant and progressive rise in the curve of the number of patients in the hospital during October and the early part of November. The shortage of personnel became very acute and presented itself in the most accentuated form in the laboratory services.

The highest death rate occurred during October, when 245, or considerably more than one half of the total number of deaths occurred. During this month the deaths averaged eight per day, with three deaths as the minimum and fourteen deaths as the maximum. Of these, the majority were due to respiratory diseases. Indeed, the total number of nonwounded men among the 356 cases that came to necropsy was 214, or in excess of 60 per cent.

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The important findings will be discussed in the order of their frequency. (See appended statistical résumé.)

#### EMPHYEMA AND PLEURISY

The most frequent necropsy finding in the entire series was empyema and pleurisy. This occurred in 63.2 per cent. of the series. The degree of pleurisy varied from a few cubic centimeters of serofibrinous exudate to several liters of thick pus. In most of the cases there were fibrinous deposits, occasionally large, shaggy, fibrinopurulent masses. The distinction between empyema and plain pleurisy was at times made only arbitrarily, depending on the quantity and character of the exudate. Real thick creamy pus was of rare occurrence, being present in only about twenty of the cases. The remaining thirty cases classified as empyema were characterized more by a thin, only slightly turbid, serous exudate, containing large fibrinopurulent masses. The abundance of this plastic, shaggy exudate was very striking. It was not at all unusual to find a yellowish-fibrinous deposit from 3 to 4 c.c. in thickness, covering the lower lobes of the lungs. Rarely was the exudate blood tinged. A number of the true empyemas were associated with gunshot wounds of the chest.

Of the "nontraumatic" empyemas, only about 50 per cent. of the cases were diagnosed clinically. In a few cases in which thoracostomy was performed, the drainage tubes were found inserted 2 to 4 inches into the chest cavity, so that from 500 to 1,000 c.c. of pus were still undrained.

Subacute or chronic pleurisy was encountered fifty times, or in 14 per cent. of the cases. A combination of both chronic and acute pleurisy existed in thirty cases, or 8.5 per cent.

The terms "chronic" and "acute" are often misnomers. We term lesions with fibrous adhesions as chronic. Yet these may be of only short duration. A case came to necropsy which demonstrated how quickly these adhesions may arise. A man was wounded by a piece of shrapnel in the chest and was sent to the hospital with a diagnosis of a foreign body in the lung as revealed by the roentgen ray. In the hospital the roentgen ray confirmed the diagnosis until about one day before death, which was twenty-two days after the injury. A roentgenogram taken at this time in a changed position of the patient showed the bullet movable in the pleural cavity. At necropsy there was found a localized empyema in the pus of which was present a small piece of shrapnel. The adhesions walling off this empyema were exceedingly strong and along the entire margin of the "abscess" cavity there were dense, hyalinized, grayish white, connective tissue adhesions, 3 mm. in thickness, which abruptly thinned out over the uninvolved portions of the lung

and pleura. The involved portion of the pleural cavity occupied about two thirds of the space on that side; the rest was entirely normal. The other pleural cavity was also free from lesions. Here, then, was a lesion with dense fibrous connective tissue formation, 3 mm. in thickness, which formed during the short period of twenty-three days.

#### PNEUMONIA

The next most frequent finding was pneumonia. This condition was present in 218, or 61.2 per cent. of the cases. The intensity of the involvement varied from almost miliary areas of consolidation around the bronchioles, to complete hepatization of entire lobes on one or both sides. Bronchopneumonias were most common, constituting more than three fourths of the cases. These at times were so massive and confluent that they resembled true lobar pneumonias. Some of the cases diagnosed at necropsy as lobar pneumonia, which later proved to be streptococcic infections culturally, were probably of this type.

Cultures and smears from the lungs were taken frequently. The cultures were made by searing the cut surface thoroughly and then, with a glass pipet having a rather large opening, a small quantity of macerated pulp, mixed with expressed fluid, was drawn up and inoculated into appropriate media. The maceration was accomplished by working the end of the pipet up and down into the parenchyma through the sterilized surface.

The frank characteristic lobar pneumonias in the gray hepatization or early resolution stage, as found ordinarily, were very uncommon. Not more than twenty such cases were encountered. The other cases classified under lobar pneumonia were atypical. An entire lobe or even an entire lung was often involved, but this involvement was irregular. The organ, though solid and heavy, was not large, and the cut surfaces were very mottled showing grayish, brownish or dark red areas of hemorrhage and edema with small portions that would still float in water. Areas of necrosis with abscess formation were quite frequent.

One type of pneumonia was encountered that was different from all ordinary pneumonias. In this type the involvement was either of an entire lobe or only of portions of one or several lobes. The involved areas were firm, heavy and had a rubber resiliency. The cut surfaces were dark red or dark brown in color, often showing a mottling with miliary or submiliary yellowish areas. Sometimes there was a fine grayish lace work visible through the reddish parenchyma that suggested thickened alveolar walls. These areas seemed to be most prominent along the bronchial branches. Culturally this type of pneumonia gave invariably a streptococcus, either hemolytic or nonhemolytic.

Microscopically, in the earlier stages, the alveolar walls show a thickening and an infiltration with lymphoid and plasma cells. The alveoli contain serum, red blood cells, a few polymorphonuclear leukocytes and many desquamated epithelial cells. The walls are edematous and the capillaries are dilated. Some show an intense infiltration with polymorphonuclears. In the later stages, the alveolar walls are seen invading the fibrinous plugs in the alveoli. The alveolar walls themselves appear like dense cellular bands of connective tissue, infiltrated with lymphocytes. Some areas show an almost complete fibrosis with practically all of the alveolar structure absent. Here and there may be seen alveoli lined with high cuboidal or even columnar epithelium suggesting attempts at regeneration. The last stage of this pneumonia is identical with the typical chronic, organizing or indurative pneumonias of the textbooks.

The histories in these cases were not at all characteristic, and did not even suggest the type of lesion present. Some cases had a rather acute onset with a history of not much more than a week's duration. Others presented histories extending over two, three or sometimes four weeks.

The frequent gradations from one type of pneumonia to another and the occasional mixture of all the types in a single lung, made it very difficult at times to classify properly the lesions encountered. Histologic study has occasionally demonstrated the existence of interstitial pneumonia where no such diagnosis was made at necropsy grossly; and conversely some cases diagnosed as interstitial pneumonia proved to be only a massive bronchopneumonia with extensive edema and hemorrhage accompanied by very little purulent exudate.

#### HEART'S BLOOD CULTURES

Blood cultures were taken routinely at all necropsies. The anterior surface of the right ventricle was sterilized with a pronged searing iron and about 5 c.c. of blood removed with a sterile glass pipet. This was inoculated into two or three tubes of dextrose broth. Sometimes a portion of this mixture was plated out in the laboratory. Pneumococci were tested for bile solubility.

The number of positive cultures was high, about 50 per cent. This is considerably higher than in civil life experience. Of this number more than one half showed *S. hemolyticus*. Not a single case of a true *S. viridans* was obtained. The one pure culture of this organism identified came from a blood culture taken a few days before death in a case of septicemia.

*B. welchii* was recovered through blood culture from several cases in which no gaseous gangrene was present, and from two patients who were not even wounded. The *B. pyocyaneus* was recovered twice in pure culture and three times mixed with other organisms.

## GUNSHOT WOUNDS

About 40 per cent. of the cases in this group came to necropsy. This included minor as well as major injuries. In a number of these cases, the wounds had nothing to do with the actual cause of death. The extremities suffered the largest number of injuries. Fractures of the femur and the ilium contributed to death most frequently outside of the direct injuries to the peritoneal cavities which resulted in general peritonitis. Under injuries to the chest were included injuries to the dorsal spine as well as to the thoracic cavity. Every case of spinal cord injury resulted in extensive gangrenous and ulcerative cystitis.

Striking features in the cases of head injuries were the finding of massive destruction of brain tissue in cases up to six weeks after the inception of the injury. More than once, the question that arose in the mind of the pathologist was not why did the patient die or what caused his death, but why did he or how could he live so long?

In many of the gunshot injuries the infection was very great, causing dissecting abscesses to extend up and down the tissues from the point of injury. Sometimes several square feet of skin and muscle tissue were undermined by the spreading infection. In many cases, at the time of necropsy, it appeared that the surgical treatment was altogether too conservative. Often the debridement was not extensive enough, while in other cases a limb was saved at the expense of a life.

## OTITIS MEDIA AND SINUSITIS

Very early in the postmortem examinations the presence of pus in the sinuses of the skull was a striking feature. It was most constantly present in cases in which pneumonia was the prominent lesion. When only one sinus was involved, it was usually the sphenoid. One fourth of all the cases showed purulent sphenoidal sinusitis and frequently the pus "welled" up, as soon as the sinus was opened. Otitis media was relatively infrequent and when present contained exudate in a much lesser degree.

Smears and cultures from the pus frequently showed no organisms. When organisms were present they usually corresponded to those found in the cultures from the heart's blood or from the lung. Streptococci and pneumococci were therefore the most common bacteria. The *B. influenza* of Pfeiffer was exceedingly rare, being found in only one case of sphenoidal sinusitis.

The question of etiology is an interesting one. Were the broncho-pneumonias, so frequently encountered, secondary to the sinusites, or were the sinusites secondary to the pneumonias? The possibility of a "reversible" reaction has to be admitted. Infected material from the

sinuses might drain down the pharynx and through the larynx gain entrance to the terminal bronchioles where it might set up a purulent bronchitis and a subsequent pneumonia. But the reverse may also occur. A patient in bed with bronchopneumonia cannot help getting the nasopharynx bathed in sputum from whence infection may spread to the sphenoidal and ethmoidal sinuses. Our necropsy material did not aid in clarifying this relationship, since priority in either lesion could not be established. On a few occasions it was thought that the sinusites appeared to be the older lesions.

#### INFLUENZA

This is not a finding at necropsy; but under this heading are discussed the lesions found at necropsy in eighty-seven cases in which the diagnosis of influenza was present on the field medical card as the cause of the patient's admission to hospitalization. Probably some of these cases were diagnosed wrongly; perhaps some patients died as a result of complications of influenza in which the proper initial diagnosis was not entered.

Of the eighty-seven cases so diagnosed, 86.2 per cent. showed complicating pneumonias. These pneumonias were not greatly dissimilar to other pneumonias except in a few details. First, the percentages of lobar and interstitial types are higher in this group than in the total pneumonias. This may be accounted for by the fact that in these cases the pneumonias played a more important rôle in the causation of death than in the others, since in the total pneumonias many of them were only terminal conditions, secondary to severe wounds, typhoid fever, etc. The percentage of identified pneumococcus pneumonias is also higher.

Abscesses were more frequent. Dilatations of the bronchioles and bronchi were fairly common. Some of the sacculations measured several centimeters in diameter. Some structures that appeared like abscesses were proved on closer observation to be bronchiectases of the saccular type.

Parallel with the high percentage of pneumonias ran the high percentage of sinus involvement. Fifty out of the eighty-seven cases showed this condition.

Meningitis was found in 8 per cent. of the cases admitted as influenza. One of these was a tuberculous case. This may have been a mistaken initial diagnosis, since the early symptoms of the tuberculous meningitis might have simulated influenza. The two cases of pneumococcic meningitis were secondary to pneumonia and empyema, which in turn were probably secondary to influenza. With the four cases of meningococcic meningitis it is difficult to decide whether the influenza

actually antedated the meningococcic infection or whether there was a mistaken initial diagnosis. It has been stated that influenza may increase the susceptibility to meningeal infection, especially meningococcic.

One of the negative findings is worth mentioning—the almost complete absence of recently activated tuberculous lesions by preexisting influenza, a complication frequently mentioned in the textbooks. Reference to the attached statistical résumé will show that the percentage of occurrence of this lesion in the cases of influenza was less than half of that found in the total number of necropsies.

The other associated lesions, such as Zenker's degeneration, septicemia, pericarditis, etc., need no special discussion here. Their frequency can be found by referring to the statistical summary accompanying this paper.

A few bacteriologic reflections may be relevant at this point. A careful study of the material, both from the pathologic appearances and from the bacteriologic findings, suggests that the influenza bacillus of Pfeiffer did not play an important rôle in the cases of influenza treated at this center. Out of a total number of 356 necropsies, only three cases revealed a bacillus in cultures or in smears which morphologically and culturally resembled the *B. influenzae*. This was found in one case in smears and cultures of the lung; in another, in smears and cultures from the sphenoidal sinus, and in a third, in cultures from the blood. In these three cases the organisms were present not in pure culture but mixed with pneumococci. Although in a large majority of the cultures made at necropsy, the conditions were favorable for the growth of the influenza bacillus, nevertheless this organism revealed itself very rarely. Neither was it found in direct smears from the pus in the sinuses nor from the lungs. It might be argued that the cases which came to this center were somewhat late in the stage of the disease, and that this fact might explain the absence of the true causative agent and the presence of the secondary invaders. But a casual study of the literature on this subject tends to show that similar findings are not uncommon in many of the laboratories throughout the world. Careful bacteriological studies in some of the camps of the United States have almost convinced the investigators that the *B. influenzae* plays a very unimportant rôle, if any, in the etiology of influenza.

Considering the method of spread, the kind of complications and the character of the lesions found at necropsy, influenza may be considered as a highly contagious, but self-limited disease of unknown etiology, which bears a remarkable resemblance to measles. Indeed, it is convenient to look on influenza as nonexanthematous measles. There are several reasons for such a concept; the extreme contagious-

ness of both diseases associated with coryza, pharyngitis and lacrimation; the inability to demonstrate definitely the causative agent; the relative absence of leukocytosis, which is especially striking as the onset of the complicating pneumonias; the frequency of the pneumonic complications which are nearly always the cause of death in these diseases; the gross and microscopic appearance of the lesions in the lungs, bronchi and bronchioles with the occasional production of interstitial pneumonias and the frequent bronchiectases. It is common knowledge that one of the important etiologic factors of bronchiectasis is measles. And those who perform necropsies in cases with antecedent influenza histories are forcibly impressed with the frequency of the irregular fusiform and saccular dilatations of the bronchi and bronchioles. (In this connection it will be interesting to follow up the cases of influenza leading to convalescence and see the frequency of chronic bronchiectases that will reveal themselves later.) Just as measles predisposes the individual to secondary invasions of the respiratory tract, as a result of pathologic changes occurring in the epithelium of the tracheobronchial tree, so also it would seem that influenza produces not unlike changes which greatly facilitate secondary invasion by organisms such as the streptococcus, pneumococcus or *B. influenzae*. It seems reasonable to assume that the type of invasion depends to a great extent on the type of organism present in the throats of large numbers of individuals in any given locality. In places where the influenza bacillus is prevalent, this organism will be found in the associated inflammatory conditions. In districts where a certain type of pneumococcus is present, the pneumococcus will be found as the principal invader. In areas where the hemolytic streptococcus is the inhabitant of the throat in a large percentage of the patients, the hemolytic streptococcus will be found in the lungs, pleural cavities and other organs or tissues of the body.

While carrying on investigations in this laboratory on the spread of diphtheria by means of the hands and fomites,<sup>1</sup> the results suggest that the rapid spread of influenza may, to a very large degree, be due to extensive contamination of the hands and fomites with the virus. This contamination is due to the fact that nearly all the cases of influenza present more or less pharyngeal involvement and coryza; conditions which necessitate the frequent use of handkerchiefs, and these consequently soon become saturated with the secretions. Thus the hands of the patients remain persistently contaminated—a condition which even the rigid discipline of the doctors and nurses cannot prevent. There is practically no disease, with the exception of the "com-

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1. Barron, M., and Bigelow, G. H.: Diphtheria at a Hospital Center, J. Infect. Dis. **25**:58 (July) 1919.

mon colds," which has a greater chance of perpetuating an almost continuous state of contamination of the hands than does influenza during the early, acute stage of the disease.

The study of influenza at this center emphasizes the fact that the etiology of this disease is as yet unknown. The great diversity of findings in different laboratories throughout the world makes it reasonable to assume that a filtrable virus is most probably the etiologic factor. This organism, whatever it may be, would produce in most cases only a self-limited disease were it not complicated by the secondary invaders such as *Streptococcus hemolyticus*, pneumococcus or *B. influenzae*. This invasion is consequent to a lowering of the barrier in the epithelium of the respiratory tract by this unknown agent. The disease is spread by nasal and pharyngeal secretions and probably also through the conjunctivae. Hands and fomites probably play a very important rôle. It would seem that from a clinical standpoint effort should be directed, for the present at least, not so much to prevent the spread of influenza, which is so difficult, but to prevent the entrance of the secondary invaders which nearly always are responsible for the seriousness of the disease and for death, when the latter occurs.

#### NEPHRITIS

Acute parenchymatous changes of the kidneys were relatively frequent, occurring in about one fifth of the cases. However, about one half of these cases were very mild. Fairly definite lesions were present in about 11 per cent. of all cases. No characteristic gross kidney lesions were noted in cases of uncomplicated gaseous gangrene. Lesions sufficiently pronounced to cause death were encountered only twice, or in 0.6 per cent. It was gratifying to note how very few definitely chronic lesions of any kind had escaped the observation of the Army examining boards when recruiting was in progress.

#### PERITONITIS

Peritonitis was encountered forty-one times. Of the thirty-seven cases of acute peritonitis, twelve were attributable directly to gunshot wounds. Several of these patients were definitely not transportable and died soon after their admission to the hospital. One case of peritonitis had an unusual and obscure etiology. There was found a complete rupture of the ileum a short distance above the ileocecal valve. The intestine was completely severed as if by a pair of scissors. The ends were black and necrotic for a distance of a few millimeters. The healthy portion of the intestinal wall stopped abruptly. The mesentery opposite the rupture was thickened and indurated. On the superior

surface, at a point 2 cm. above the intestinal attachment, there was an ulcer, 15 mm. in diameter and 5 mm. in depth, involving a lymph node. The base and walls were necrotic and covered with purulent exudate. The upper surface of the intestinal coil had curled upward, plastering itself firmly to the mesentery and covering the lower margin of the ulcer. It apparently was Nature's vain attempt to prevent the rupture of the suppurating lymph node into the peritoneal cavity. On the inferior surface of the mesentery opposite this ulcer there were strong fibrous adhesions binding the mesentery to the brim of the pelvis. The rupture of the intestine probably resulted from this inflammation and ulceration, completely cutting off the blood supply of one small segment with the resulting rupture. The cause of the suppuration of the lymph node could not be determined.

#### GAS INHALATION

Of the patients who died, 10.9 per cent. gave a history of gassing. Nearly all were cases of mustard gas inhalation and contact. The pathology of these cases was studied in greater detail by a member of the Central Laboratory staff.<sup>2</sup> All gradations of lesions were found, from acute congestion of the mucosa covered by a thin fibrinopurulent exudate to that of a severe fibrinopurulent tracheobronchitis with ulceration. The most advanced cases presented numerous ulcers through the mucosa of the trachea and bronchi with extensive destruction of tracheal cartilages. There were large areas of gangrene with abscess formation in the lung. Nearly all of the advanced cases showed abscesses and gangrene of the lungs. The exudate in the larynx was generally very pronounced, and often diphtherial in appearance, so that on several occasions there resulted confusion in diagnosis.<sup>1</sup> The complicating pneumonia was always of the bronchogenic type. Hemorrhages into the lungs were common.

#### PULMONARY TUBERCULOSIS

Of the thirty-six patients (10.1 per cent.) showing pulmonary tuberculosis, 66 $\frac{2}{3}$  per cent. had chronic or healed lesions. These presented simply old scars or fibrosed nodules at the apices, most often on the right. Caseating and calcareous nodules were sometimes present. Of the twelve cases of acute, or acute and chronic, tuberculosis, only a few had lesions extensive enough to be factors in the final exitus. In practically no case could tuberculosis be assigned as the primary cause of death.

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2. Covey: Pathology of Mustard Gas Inhalation, *Am. J. M. Sc.* **157**:808 (June) 1919.

## SEPTICEMIA

Nine per cent. of all cases had gross evidences of septicemia at necropsy in conjunction with antemortem as well as postmortem positive blood cultures. Three fourths of the cases were due to *Streptococcus hemolyticus*. The most constant findings in these cases were extensive jaundice of the skin and conjunctivae, together with subepicardial and subpleural petechial hemorrhages.

## MENINGITIS

Altogether, twenty-two cases of meningitis came to necropsy. Exactly one half of these were meningococcic in origin. The mortality of this form of meningitis was very unsatisfactory in spite of the energetic treatment with large quantities of serum.<sup>3</sup> Three cases were due to pneumococci, two of which occurred with an initial history of influenza. All three cases were superimposed on pneumonias or empyemas. In one case, the spinal fluid was very turbid, and direct smears of the uncentrifuged specimen revealed the pneumococcus in numbers comparable to those found in twenty-four-hour cultures. Typing revealed the pneumococcus to belong to Group II.

There was one case of tuberculous meningitis. The diagnosis was made shortly before death by finding tubercle bacilli in the fluid. At necropsy, there was found, in addition to the advanced meningitis, tuberculosis of the kidneys and bladder and tuberculous caries of the eleventh dorsal vertebra. Nothing but a shell of the body of the vertebra remained. This was wholly unsuspected, since it had given no clinical symptoms.

The seven other cases in the series were mostly streptococcal, and were consequent to traumatic lesions of the brain and spinal cord.

## ANEMIA FROM HEMORRHAGE

Severe secondary anemias, sufficient to produce symptoms and death, were found in 4.5 per cent. of the cases. In a few of these, the anemias were complicated by septicemias. The majority of the uncontrollable hemorrhages followed ruptures, through gunshot wounds, of the femoral and gluteal blood vessels. One patient died of hemorrhage from the internal maxillary artery which continued to bleed even after the common carotid on that side had been ligated.

## GAS GANGRENE

Gas gangrene was present in fifteen cases. When the organism was identified, it nearly always proved to be the *B. welchii*. In no case was

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3. Bigelow: Nonepidemic Epidemic Meningitis, Arch. Int. Med. **23**:723 (June) 1919.

the *B. edematiens* recovered, although several of the cases presented gross lesions—very extensive edema with very little gas in the tissues—characteristic of the bacillus of toxic edema. In antemortem examinations of wound anaerobes, the *B. vibrion septique* was identified in five cultures. The brownish red, dry, very friable, crepitating muscles produced by the *B. welchii* was very characteristic and easily identified.

#### PERICARDITIS

Pericarditis was present in 3.9 per cent. of the cases. In several cases there was present a purulent or fibrinopurulent exudate to the extent of a liter or more within the pericardial cavity. Yet, with perhaps one or two exceptions, no antemortem diagnoses of the condition were made. It doubtless proved, relatively at least, the greatest diagnostic pitfall.

The chronic pericarditides were of the adhesive type. The chronic "patchy" epicarditis—the so-called "soldier spots" of some writers—were very interesting because of their frequency. Unfortunately, they were so common, that not sufficient attention was paid to them. They were encountered many times more frequently than in civil life. Many stages in their development could be traced out. There were some with a patch about 2 cm. in diameter situated over the right ventricle anteriorly, several centimeters above the apex. From this patch, a bundle of white, coarse adhesions, 2 cm. in length, extended, uniting it with the corresponding surface of the pericardial wall. The next stage found was where the adhesions were already ruptured showing a large tuft of adhesions hanging free from the epicardium and a smaller tuft of adhesions projecting from the pericardial sac. The next stage showed a rough, thickened epicardial patch with no or only a few very short tags present. The corresponding surface on the pericardium showed slight evidences of adhesions or thickening. The last stage showed a simple, opaque, glistening, white, thickened patch of the epicardium. There were no more evidences of any lesions on the corresponding point of the epicardium.

#### ENTEROCOLITIS

Twelve, or 3.3 per cent., of the cases showed lesions in the large and small intestines other than those resulting from typhoid fever. Of these twelve cases, three were due to *Endameba dysenteriae* in which the parasites were demonstrated in preparations made from the ulcers. Two cases presented classical pictures of bacillary dysentery. The involvement was principally in the colon, but extended also for a considerable distance up into the ileum. The crests of the folds of

mucous membrane were covered with thick, dull layers of exudate. The mucosa was edematous and hemorrhagic. Numerous ulcers were present which in some areas were so extensive as to leave only islands of polypoid patches of mucous membrane. Cultures were taken from the feces and heart's blood, but not from the spleen or mesenteric lymph nodes, and this may account for the negative bacteriologic evidences for the identification of the lesions. Seven cases had extensive lesions in which neither endamebae nor *B. dysenteriae* were demonstrated, and the gross pictures of the ulcerations were not sufficiently characteristic to make a definite diagnosis. Not a single case of *B. dysenteriae* of any type was isolated at this center, although numerous cultures were made of suspected stools. Typhoid and paratyphoid organisms were occasionally isolated both from the feces and from the urine, as well as from necropsy material.

#### ZENKER'S DEGENERATION

Parenchymatous degeneration of the recti muscles with hemorrhage and rupture was strikingly frequent. Several of the cases were frank cases of "Zenker's" degeneration, both grossly and microscopically. The others showed the swelling of the muscle fibers, the hemorrhage and rupture of the muscle bundles, but the yellowish "waxy" appearing areas were not so prominent grossly.

Seven of the nine cases were associated with pneumonia following a history of influenza. In one of these there was also present a hemorrhagic encephalitis. Of the two remaining cases, one was associated with pneumonia complicating gunshot wound, and the other with pneumonia in which the initial diagnosis was not stated. Not a single case of typhoid presented this lesion, although typhoid is considered in the textbooks as being the principal disease in which it is found.

Several interesting confusing diagnoses resulted from the hemorrhage and rupture of the abdominal rectus muscles. In one case a diagnosis of appendicitis was made which was fortunately treated medically and not surgically. At the necropsy the appendix was found to be normal, but the lower third of the right rectus muscle showed typical Zenker's degeneration with rupture. In another case, the patient suddenly developed signs of acute cholecystitis. All his symptoms were referred to the gallbladder region. There was marked tenderness, severe pain, some rigidity and a distinct mass was palpable. An area of dulness the size of an orange, in the region of the gallbladder, was outlined. The findings were so definite that it was decided to operate, but not until a careful consultation was held. A diagnosis of acute cholecystitis, probably suppurative, was made. On the day set for operation, the patient developed edema of the lungs and sank into a

condition too serious for operation. He died several days later. At necropsy, the gallbladder was found to be entirely normal, and this time the upper right rectus muscle showed Zenker's degeneration with rupture and extensive hemorrhage into the sheaths which extended upward to the insertions at the costal cartilages. The greatest amount of blood clot was found just below the costal margin.

One point of differential diagnosis between these lesions in the rectus muscles and true surgical conditions within the peritoneal cavity was brought out at a discussion in one of the clinicopathologic conferences. Whereas tenderness and pain is elicited readily by very superficial palpation in the first instance, it is only on deeper palpation that the maximum discomfort is produced in the latter case.

#### TYPHOID FEVER

In this series eight cases of typhoid fever were encountered. Only one or two were diagnosed clinically. The lesions in the intestines were characteristic, but extensive ulcerations in the colon were more frequently encountered than is the usual experience. In most of the cases, the *B. typhosus* was recovered from the spleen, gallbladder and the heart's blood. A few cases failed to give any bacteriologic evidences of the disease although the gross lesions were definitely diagnostic.

The clinical diagnosis of typhoid and paratyphoid fever proved quite a problem. In many cases at the center which were clinically typhoid, no corroborative laboratory evidences could be obtained either in positive blood cultures or in positive stool or urine cultures. The ordinary Widal test is, of course, worthless in prophylacticated individuals. One of the laboratory staff<sup>4</sup> obtained interesting results by using Dryer's quantitative agglutination, which promises to be a valuable aid in differential diagnosis of this disease in prophylacticated individuals, where cultural evidences are negative. No known case of paratyphoid fever came to necropsy.

#### DIPHTHERIA

The mortality from diphtheria was very disappointing. Several patients dying of diphtheria came to necropsy with the case undiagnosed clinically. The reasons for this are discussed fully by Barron and Bigelow.<sup>1</sup> All cases were of the laryngeal type—a condition rather unusual for adults.

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4. Eggerth: A Study of Dreyer's Agglutination Technique in the Army, J. Infect. Dis., 1919 (in press).

## HEMORRHAGIC ENCEPHALITIS

Three cases of hemorrhagic encephalitis are included in the series. One case was associated with ascending myelitis associated with complete transverse laceration of the lower dorsal cord following gunshot injury. Another case was associated with pneumonia following a history of influenza. The third case was associated with a beginning bronchopneumonia in a patient who had apparently completely recovered from a gunshot wound. The patient was ready for evacuation when he became sick very suddenly with a high temperature, rapid pulse and increased respiration. The next morning after his readmission to the hospital, a diagnosis of lobar pneumonia was made. Shortly afterward, he developed symptoms of increased intracranial pressure, with subnormal temperature, pulse 46, respiration 8. Retinoscopy revealed a "choked disc." He died less than forty-eight hours after admission. At necropsy there was extreme injection of the pia mater and the arachnoid membrane. Section of the brain showed the white matter peppered with pinpoint to pinhead sized hemorrhages most marked in the corpus striatum on the left side, the corpus callosum and in the pons. The lungs showed only the very earliest stage of bronchopneumonia. The blood culture made at necropsy was sterile. Unfortunately no cultures were made from the brain tissue.

## CONGENITAL ANOMALIES

Of the fourteen prominent congenital anomalies, exactly 50 per cent. involved the kidneys. There were three cases of horseshoe kidney. Two cases of hypoplasia were found in which the involved kidneys were about the size of lima beans, while the kidneys on the opposite side were about twice the normal size, a compensatory hyperplasia. There were two cases of complete aplasia of one of the kidneys. In these, not only was there no vestige of kidney substance found, but there was not a trace of the corresponding ureter.

Of the remaining anomalies, only one other is worthy of mention, that of an accessory lung. A mass of tissue entirely covered with pleura, having the size, shape, appearance and consistency of one of the lobes of a lung in a full term fetus, was found in the left pleural cavity attached by a narrow pedicle of connective tissue to the antero-lateral prevertebral tissue in the region of the eighth dorsal vertebra. This pedicle appeared like the structure of the hilus of a lung, but had no relation to any of the structures of the normal lung. The only connection discovered between it and the normal structures was through two arteries, each about 2 mm. in diameter (outside), arising from the aorta in that region. These arteries were, of course, entirely

anomalous. The parenchyma did not crepitate and contained no air. On section, a miniature bronchial tree could be identified in which the structure corresponding to a bronchus measuring about 5 mm. in diameter ended blindly and bluntly in the loose cellular tissue of the "hilus" near the two arteries. Microscopically, the tissue shows definite bronchial and bronchiolar structure, with cartilages, non-striated muscle fibers and connective tissue. The blood vessels are prominent. The lumen is lined with a high columnar epithelium and contains mucoid material mixed with epithelial cells and other cellular debris. The parenchyma shows a rather loose cellular connective tissue through which are scattered islands of cuboidal and columnar epithelial cells, some thrown together irregularly, others arranged in gland-like structures. This tissue will probably be studied more in detail by me at some future time.

#### SUMMARY

A number of important facts reveal themselves in the study of this material. A few of them are the following:

Empyemas and acute pericarditides are not so readily diagnosed as the textbooks would make one believe. These conditions have proven pitfalls for some of our best diagnosticians.

A very large percentage of the pneumonia cases have associated suppurative conditions in one or more of the sinuses in the skull. These present very meager, if any, clinical evidences, and nearly always remain undiagnosed until the postmortem examination.

Influenza practically never kills by itself alone. In the present series, pneumonia was the cause of death in nearly all of the cases, a few patients dying of meningitis, typhoid fever, etc. *B. influenzae* of Pfeiffer played no important rôle.

Of all the deaths, about 75 per cent. were medical. Although almost 40 per cent. of the deaths occurred in wounded persons; in a considerable proportion of these the wounds were far too slight to play any important part in causing death.

The surgical treatment of gunshot wounds was at times not sufficiently intensive. Cases came to necropsy which probably might have been saved by amputation of an involved extremity, or by more radical debridement.

Some surgical cases with gunshot injuries to the abdomen were evacuated to base hospitals while in a nontransportable condition.

Zenker's degeneration, with rupture and hemorrhage, is associated with highly virulent infections. It sometimes may cause confusion in diagnosis from intra-abdominal surgical conditions.

Congenital anomalies were present in about 4 per cent. of the cases, and one-half of these involved the kidneys.

Practically no well established chronic lesions escaped the detection of the recruiting medical examining boards.

## RÉSUMÉ OF THREE HUNDRED AND FIFTY-SIX NECROPSIES

Statistical Data Up to Jan. 1, 1919

### GENERAL CONSIDERATIONS

Total number of patients treated.....	29,196
Total number of deaths.....	429
Mortality rate.....	1.47 per cent.
Total number of necropsies.....	356

	Patients Treated*	No. of Deaths	Mortality Rate, %	No. of Necropsies
Evacuation Hospital 19.....	4,951	7	0.14	7
Base Hospital 26.....	5,512	99	1.79	85
Base Hospital 25.....	5,860	117	1.99	97
Base Hospital 49.....	4,626	84	1.81	76
Base Hospital 56.....	7,766	82	1.05	67
Base Hospital 70.....	5,371	40	0.78	24

Date of first convoy of patients to center..... July 23, 1918

Date of first necropsy..... July 26, 1918

### NECROPSY FINDINGS

Empyema and pleurisy.....	225 cases or 63.2%
Acute pleurisy.....	95 cases or 26.7%
Empyema.....	50 cases or 14.0%
Chronic pleurisy.....	50 cases or 14.0%
Chronic and acute pleurisy.....	30 cases or 8.5%
Pneumonia.....	218 cases or 61.2%
Bronchopneumonia.....	165 cases or 75.5%
Streptococcic.....	64 cases or 38.8%
Pneumococcic.....	20 cases or 12.1%
Undetermined.....	81 cases or 49.1%
Lobar pneumonia.....	37 cases or 17.0%
Pneumococcic.....	16 cases or 43.2%
Streptococcic.....	11 cases or 29.8%
Undetermined.....	10 cases or 27.0%
Interstitial.....	16 cases or 7.5%
Streptococcic.....	16 cases or 100%
Positive blood cultures.....	163 cases or 45.8%
Hemolytic streptococcus.....	84 times or 51.4%
Nonhemolytic streptococcus.....	35 times or 21.3%
Pneumococcus.....	26 times or 16.0%
<i>B. welchii</i> .....	12 times or 7.3%
<i>B. pyocyaneus</i> .....	5 times or 3.4%
Staphylococcus.....	1 time or 0.6%
Number of wounded.....	142 or 39.8%
Parts wounded.....	163
Extremities.....	86 or 52.7%
Abdomen.....	28 or 17.1%
Chest.....	26 or 16.0%
Head.....	23 or 14.2%

\* This total includes 4,890 patients received by transfer.

Number of bones fractured.....	91	
Ribs .....	13	
Femur .....	12	
Ilium .....	10	
Vertebrae .....	10	
Skull .....	9	
Tibia .....	7	
Fibula .....	4	
Scapula .....	4	
Humerus .....	3	
Cocciix .....	3	
Radius .....	3	
Ulna .....	3	
Ischium .....	3	
Metacarpal .....	2	
Sacrum .....	2	
Ankle .....	1	
Clavicle .....	1	
Jaw .....	1	
Number of cases with otitis media and sinusitis.....	120	or 33.7%
Number of otitis media and sinusitis involvements.....	192	
Sphenoidal sinusitis.....	92	times or 25.8%
Frontal sinusitis.....	34	times or 9.5%
Ethmoidal sinusitis.....	35	times or 9.8%
Otitis media.....	31	times or 8.7%
Influenza .....	87	cases or 24.4%
Pneumonia following influenza.....	75	cases or 36.2%
Bronchopneumonia .....	48	cases or 64%
Streptococcic .....	22	cases or 45.8%
Pneumococcic .....	14	cases or 29.2%
Undetermined .....	12	cases or 25.0%
Lobar pneumonia.....	18	cases or 24%
Pneumococcic .....	12	cases or 67%
Streptococcic .....	4	cases or 22%
Undetermined .....	2	cases or 11%
Interstitial pneumonia.....	9	cases or 12%
Streptococcic .....	9	cases or 100 %
Number of cases with otitis media and sinusitis.....	50	or 57.4%
Number of otitis media and sinusitis involvements.....	91	
Sphenoidal sinusitis.....	35	times or 70.0%
Ethmoidal sinusitis.....	22	times or 44.0%
Frontal sinusitis.....	17	times or 34.0%
Otitis media.....	17	times or 34.0%
Pleurisy .....	33	cases or 37.9%
Empyema .....	13	cases or 15.0%
Meningitis .....	7	cases or 8.0%
Meningococcic .....	4	cases or 57.1%
Pneumococcic .....	2	cases or 28.6%
Tuberculous .....	1	case or 14.3%
Zenker's Degeneration.....	7	cases or 8.0%
Pulmonary tuberculosis.....	4	cases or 4.6%
Septicemia .....	5	cases or 5.8%
Lung abscess.....	4	cases or 4.6%
Pericarditis .....	3	cases or 3.4%
Typhoid fever.....	3	cases or 3.4%
Diphtheria .....	3	cases or 3.4%
Mediastinal abscess.....	1	case or 1.2%
Encephalitis, hemorrhagic.....	1	case or 1.2%
Abscess of kidney.....	1	case or 1.2%
Nephritis .....	76	cases or 21.3%
Mild .....	34	cases or 9.5%
Moderate .....	40	cases or 11.2%
Severe .....	2	cases or 0.6%

Peritonitis .....	41 cases or 11.5%
Acute .....	37 cases or 90.0%
Peritonitis from gunshot wound.....	12 cases
Chronic .....	4 cases or 10.0%
Gas Inhalation and Contact.....	39 cases or 10.9%
Tracheobronchitis and pneumonia.....	26 cases or 66.6%
Tracheobronchitis .....	10 cases or 25.6%
Pneumonia .....	3 cases or 7.8%
Tuberculosis, pulmonary.....	36 cases or 10.1%
Chronic or healed.....	24 cases or 66.7%
Acute .....	8 cases or 22.2%
Chronic and acute.....	4 cases or 11.1%
Septicemia .....	32 cases or 9.0%
Streptococcus hemolyticus.....	24 cases or 75.0%
Streptococcus, nonhemolyticus.....	7 cases or 21.9%
Streptococcus viridans.....	1 case or 3.1%
Meningitis .....	22 cases or 6.1%
Meningococcic .....	11 cases or 50.0%
Pneumococcic .....	3 cases or 13.6%
Tuberculous .....	1 case or 4.5%
Other types.....	7 cases or 31.9%
Anemia from hemorrhage.....	16 cases or 4.5%
Gas gangrene.....	15 cases or 4.2%
Pericarditis .....	14 cases or 3.9%
Acute .....	9 cases or 64.3%
Chronic .....	3 cases or 35.7%
Enterocolitis .....	12 cases or 3.3%
Amebic .....	3 cases or 25.0%
Bacillary .....	2 cases or 16.7%
Undetermined .....	7 cases or 58.3%
Zenker's degeneration.....	9 cases or 2.5%
Typhoid fever.....	8 cases or 2.2%
Diphtheria .....	8 cases or 2.2%
Hemorrhagic encephalitis.....	3 cases or 0.8%
Congenital anomalies.....	14 cases or 3.9%
Kidney, horseshoe.....	3 cases or 21.4%
Kidney hypoplasia.....	2 cases or 14.3%
Kidney aplasia .....	2 cases or 14.3%
Patent foramen ovale.....	3 cases or 21.4%
Accessory lung.....	1 case or 7.1%
Accessory pancreas.....	1 case or 7.1%
Pectoral muscle, aplasia.....	1 case or 7.1%
Meckel's diverticulum.....	1 case or 7.1%

# THE POSSIBILITIES OF PHYSICAL DEVELOPMENT IN CASES OF EFFORT SYNDROME BY MEANS OF GRADED EXERCISES \*

BERTNARD SMITH, M.D.

LOS ANGELES

Patients who show the "effort syndrome" symptom complex often have a lessened muscular strength in addition to the neurosis that is generally present. This weakness may be limited to a few muscle groups, but it is usually general and may be very marked. This was true with the men who entered this hospital from the American camps during the summer of 1918 and, because of this picture of poor muscular development, graded exercises were among the first methods adopted for an intensive study of the effort syndrome condition. Lewis and his co-workers<sup>1</sup> have used grouped exercises, requiring varying degrees of effort, in estimating the future military usefulness of these men, and, from the results, those men unfit for military service were listed earlier for discharge and the individuals retained in service were classified for duty by the grade of graduate work they could successfully carry through.

In the studies at Lakewood all effort syndrome cases on the cardiovascular wards were admitted to the exercise classes, even though the severity and persistence of the symptoms indicated a definite unfitness for any military service. In trying various forms of exercises, it was found that the confidence of the men in their ability to carry on must be secured and maintained before any efforts toward improved strength could be successful. Sharp, abrupt commands were destructive to this confidence and caused a return of overwhelming symptoms as easily as too severe work. After considerable experiment in arranging exercises for so general a reconstructive problem, the "unit system" was adopted.<sup>2</sup> The eight "units" include all muscle groups and their order is the same in each exercise grade. This report is concerned with the results from these exercises in the attempt to overcome the existing physical weakness.

An estimation of the total strength of each patient was made when he entered the hospital, and again when he was ready for discharge

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\* Report from studies made on the Cardiovascular Service, U. S. Army General Hospital No. 9, Lakewood, N. J.

\* Read before the Section on Practice of Medicine at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919.

1. Report of Medical Research Committee, Series No. 8, 1917.

2. Smith, Bertnard: J. A. M. A. 72:103 (Jan. 11) 1919.

or had completed the highest exercise grade. For these estimations the spring balance resistance test of Dr. E. G. Martin was used, the technic of which is briefly described at the end of this report. Figures for the strength of normal men in active military service were obtained from tests made on one hundred men at Camp Dix, N. J. These men had had a period of full, hard training covering from ten to fourteen months, which they had completed without symptoms. The range and average of these normal estimations are given in Table 1. It was evident from the normal figures obtained that the weight is an important factor if a comparison of strengths is to be made. Consequently, all tests have been computed for total strength (Str.) and for the ratio of strength to weight (Str./Wt.).

TABLE 1.—STRENGTH ESTIMATIONS ON 100 NORMAL MEN IN ACTIVE MILITARY SERVICE \*

Range				Average			
Strength	Weight	Str./Wt.	Age	Strength	Weight	Str./Wt.	Age
1390-2830	54.6-88.5	23.2-30.8	19-40	1655	67.6	25.6	24.1

\* All figures for strength and weight are in kilograms.

The clinical history of cases of effort syndrome among soldiers may show that the condition was present previous to entrance into military service. Others give equally definite evidence that the symptoms have developed during the period of active duty. It will be convenient to arrange the cases here reported under these two groups, according to the onset and duration of the general symptoms.

#### I. CASES WITH SYMPTOMS BEFORE MILITARY SERVICE

Of the 300 effort syndrome cases here reported, 56 per cent. give a history of symptoms having been experienced for a number of years before entrance into the army. The majority of these men have performed very little, if any, real active duty. They have found their way into a hospital or infirmary soon after induction into service.

1. *Type of Intelligence Defect.*—Among the men who give a history of this long duration of symptoms, thirty-five showed definite but varying degrees of defective intelligence.<sup>3</sup> These give differentiating characteristics that deserve attention. They are lacking in both physical and mental drive, and can be neither persuaded nor forced to do their full part in training. They have a persistently poor coordination, and go through the work of the various exercise grades with joints sagging and muscles relaxed. These men are without ambition and show a stubborn resistance to any effort that is made to change them

3. Campbell, C. Macfie: J. A. M. A. **71**:1621 (Nov. 16) 1918.

from the low economic level to which they have become adapted. Their ability to adjust themselves to a new environment, especially to military conditions, is slow and limited. The physical weakness may be extreme (Table 2), but this is not constant, and the less severe cases may have a strength that is very near normal.

TABLE 2.—COMPARATIVE STRENGTHS OF CASES OF EFFORT SYNDROME BEFORE AND AFTER EXERCISE

	No.	On Entrance to Ward			On Discharge from Ward		
		Range of Str.	Range of Str./Wt.	Average Str./Wt.	Range of Str.	Range of Str./Wt.	Average Str./Wt.
Symptoms of long duration:							
1. Intelligence defect.....	35	175-1870	3.9-24.4	15.1	780-2096	10.7-28.0	21.5
2. Physical invalidism.....	110	344-1475	6.7-22.8	14.8	883-2061	15.3-36.3	24.8
3. Unclassified.....	28	492-1619	10.8-34.0	21.0	1124-1420	18.9-36.0	26.3
Symptoms recent:							
1. After strain.....	70	600-1931	9.0-26.0	20.4	1225-2180	22.2-37.6	26.9
2. After infections*	62	593-1621	9.7-23.2	19.3	1249-1944	19.3-31.9	25.3
After rheumatic fever†.....	33	822-1706	15.3-27.4	21.3	906-2105	18.6-29.8	25.4

\* Not including cases following rheumatic fever.

† Not included in cases of effort syndrome.

Satisfactory strength estimations are often difficult to obtain in severe cases of the defective intelligence type because of the lack of cooperation. Consequently, it is doubtful if the low figures represent true strength values. In Chart 1 curves are given which show variations in strength estimations made at three periods of the same day, both at the time of entrance into the hospital and at the time of discharge. The ten curves are from estimations made on men of the defective intelligence type who had low strength readings. At the time the first observations were made the day was spent quietly on the wards or with the various routine examinations. The second group of curves are from tests made after two or more months had been spent in daily exercise classes and when the day was well occupied with educational or vocational work, together with the classes in physical training. There is a general gain in strength, but the type of curve persists. Curves obtained in the same way from the normals and from other types of effort syndrome cases are of no constant form. Ryan tests<sup>4</sup> on this type of constitutional inferiority show an early fatigue. While these individuals can advance through the exercise grades with but few symptoms and with some slight gain in general strength, the fact that they will always put the least amount of effort possible into the work is probably explanatory of the early, persistent fatigue. With the gain in general strength there is a betterment of the general health, but the mental sluggishness remains unchanged and

4. King, John T., Jr.: Arch. Int. Med. **23**:527 (April) 1919.

the men will not make any independent effort to avoid slipping back into the former condition.

2. *Type of Chronic Physical Invalidism.*—The majority of the men whose symptoms have persisted for a long time give a picture that is in rather sharp contrast to the type just considered. Here the physical weakness forms the predominant and constant picture. These men

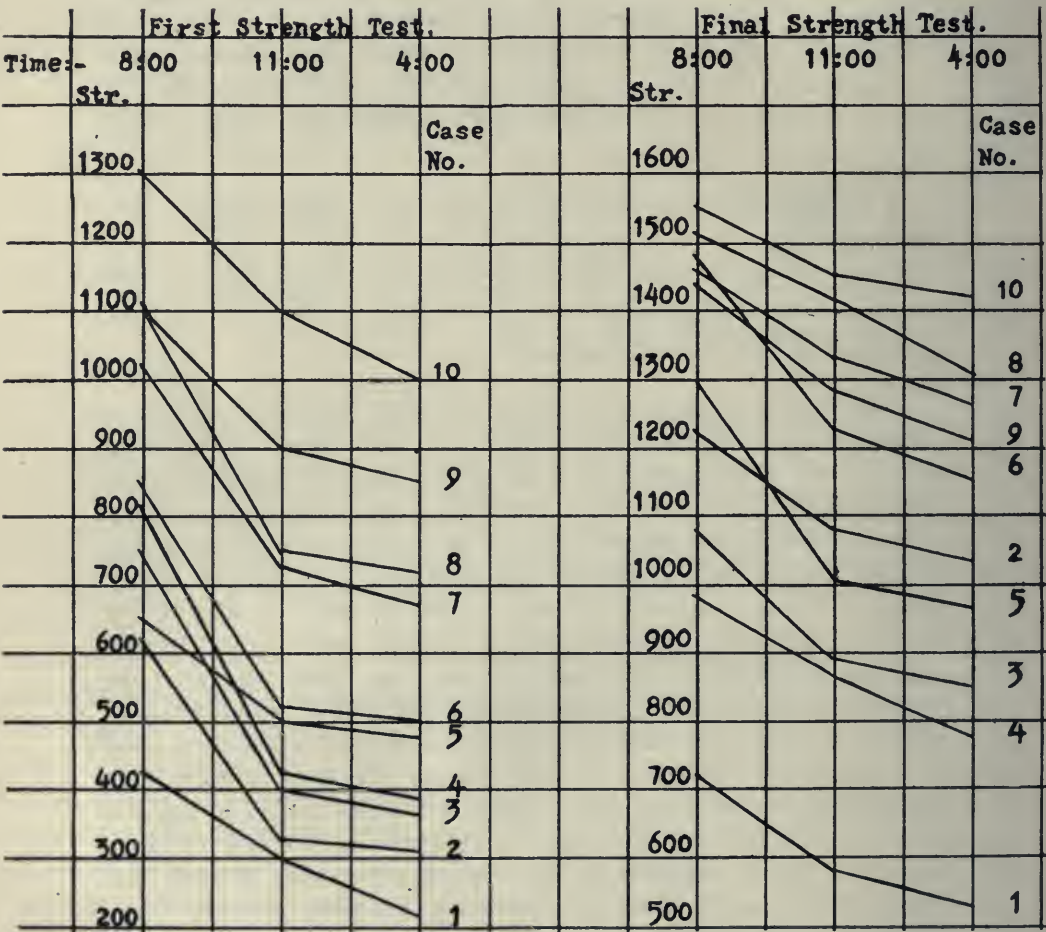


Chart 1.—Fatigue curves in severe cases of effort syndrome. Defective intelligence type. Curves from estimations of strength made before and after work in graded exercises.

have “never been strong,” or trace the beginning of the trouble to an illness in early life, frequently in infancy or childhood. A diagnosis of serious heart trouble, combined with the watchfulness of over-solicitous parents, form important contributing factors. The patients have learned to interpret the symptoms that appear after physical exertion as warnings of serious overstrain.

Since the fear of the results of this overstrain has become very magnified, it is important that physical training for these men should begin with exercises of so mild a form that no symptoms result. Advancement in the graded work must be slow and so well graduated, especially in the lower classes, that the individual is not too conscious of the increased effort demanded. Some symptoms may be experienced on beginning a higher grade which will disappear after two or three days of perseverance. Men of this type usually have a normal mentality, and such cases can be found among college and university students. Some manifestations of neurosis are usually seen in these men, but this factor is usually subordinate to the physical weakness. However, progress in the exercises may depend more on the ease with which self-confidence can be developed and maintained than on the general strength present at the beginning of the work. The man with the lowest strength of 334 kg. (Table 2) returned to duty at the end of two months, having completed all the exercise grades with a final strength of 1,658 kg. These men differ from the cases with defective intelligence, in that their cooperation is complete as soon as confidence in their own ability to carry on is restored. After they are able to take part in the more vigorous games and exercises, future progress is usually secure. The pride in their increased strength and their joy in losing the stigmata of being a weakling are sufficient to carry them ahead and should prevent them from falling back into old habits.

In the cases here reported, 110, or 37 per cent., belong to this type of physical inferiority. Of these, 84 per cent. advanced into the fifth grade of exercises in an average time of 10.6 weeks, and took part in active athletic games. The figures in Table 3 that represent the men who only reached the third and fourth grades should not be interpreted as meaning a permanent limit for these individuals. These grades were their limit only for the time they were in the hospital. Proper training after discharge should secure further improvement.

A special exercise class was formed with twenty-five patients selected from the group where symptoms were of long duration, with the desire to test the results of a more intensive training under close supervision. These men began with various forms of track work and athletic games, in addition to heavier exercises than those in the regular work for lower grades. The results with fifteen men of the chronic invalidism type are given in Table 4. The average ratio of strength to weight (Str./Wt.) on beginning work in this special class was 15.0, and, after an average of ten weeks of training, this ratio had increased to 23.6. With the 110 men who had their training in the general classes, the first strength to weight ratio averages 14.8. After an average of 10.6 weeks of work this ratio average had increased to

24.8. In the more intensive work it was definitely more difficult for the men to maintain the degree of effort required without becoming too conscious of the general effort syndrome symptoms.

TABLE 3.—TIME IN EXERCISES OF EFFORT SYNDROME TYPES, WITH FINAL GRADE REACHED

Type*		No.	Weeks in Exercises		Final Grade at Time of Discharge, with Average Str./Wt.											
					Grade I		Grade II		Grade III		Grade IV		Grade V		Grade VI	
			Range	Aver. age	No.	Str. Wt.	No.	Str. Wt.	No.	Str. Wt.	No.	Str. Wt.	No.	Str. Wt.	No.	Str. Wt.
III	1	35	10-19	12.5	1	10.7	2	14.6	2	15.4	6	17.2	9	22.4	15	25.3
	2	110	9-16	10.6	0	....	0	....	3	16.2	15	18.6	42	24.1	50	26.4
	3	23	8-13	10.5	0	....	0	....	0	....	4	19.3	10	24.4	9	25.8
II	1	70	5-13	8.4	0	....	0	....	0	....	0	....	5	24.8	65	25.5
	2	62	8-12	9.3	0	....	0	....	1	19.4	5	21.1	14	24.8	42	25.6
After R. F.		33	7-13	8.6	0	....	0	....	0	....	4	19.8	16	24.1	13	25.2

\* Group and type numbers correspond to those in Table 2.

TABLE 4.—RESULTS OF INTENSIVE TRAINING IN CASES OF CHRONIC INVALIDISM TYPE

Name	First Str.	First Str./Wt.	Weeks in Class	Final Str.	Final Str./Wt.
R. F. ....	1006	16.7	9	1240	20.6
F. W. ....	1033	18.8	9	1250	22.7
G. H. D. ....	757	12.8	12	1450	24.6
G. L. ....	1499	21.0	11	1881	25.7
E. M. ....	1141	18.3	8	1628	25.2
E. J. G. ....	689	12.5	12	1215	22.0
H. R. ....	972	14.8	9	1588	25.6
G. H. ....	830	13.3	8	1678	26.9
C. H. ....	1175	18.2	10	1445	23.9
F. P. ....	441	8.0	12	1022	18.5
R. D. ....	830	18.5	19	1220	23.5
O. S. ....	842	14.3	10	1365	23.1
S. G. ....	791	12.7	10	1334	21.6
W. H. ....	1335	20.4	13	1820	27.7
W. E. H. ....	218	4.3	9	1332	22.6
Average .....	903.7	15.0	9.9	1431.7	23.6

3. *Unclassified Type*.—In Tables 2 and 3 cases are included under “unclassified type” that had predominating nervous symptoms. Some degree of neurosis is present in all effort syndrome cases and must be recognized in a successful treatment of this condition. But there were a few men whose progress in graded work was so controlled by the nervous factor that they deserve a separate grouping. Frequent fainting attacks, complaint of severe dizziness, independent of exertion and other indications of a marked nervous instability separate these men from the other types and limit their advancement in the exercises. The general strength shows a wide variation, and there is usually no indica-

tion of a defective intelligence. These men require neuropsychiatric attention in addition to the physical training.

## II. CASES DEVELOPING SYMPTOMS DURING MILITARY SERVICE

As the period of active fighting for our troops continued, the type of cases admitted to the wards with the official diagnosis of cardiac disorder functional changed from the group with long continued symptoms to men with a greater strength in whom the condition had developed during active army duty. These patients have a previous history that is negative for the usual effort syndrome symptoms. The symptoms they present on entrance to the hospital may differ in no way from those of the more chronic group.

1. *After Nervous and Physical Strain.*—Of the 132 men who belong to this group with a recent onset of symptoms, seventy, or 53 per cent., give no etiology other than the severe nervous and physical strain of military duty. Many of these men were engaged in rather sedentary occupations in civil life, but had always considered themselves well and strong. They went through the period of training in the American camps without difficulty, and only eight of the seventy broke down during the intensive training overseas before being sent to the front. The first strength tests on these men give higher average values than are found in the cases with long continued symptoms. Also the confidence of these men in their ability to get back into condition is not so thoroughly destroyed. Many are able to advance rapidly through the exercise grades and are free from symptoms after four to six weeks of graded work. Of the seventy men, sixty-five completed all the grades of exercises without symptoms in an average time of 8.4 weeks. These men are a much milder type than are those reported by the British workers. It must be remembered that the American troops were in active fighting for a much shorter time.

2. *After Infectious Disease.*—A group of sixty-two men were admitted to the cardiovascular service with a diagnosis of a functional cardiac disorder following some infectious disease. The cardiac symptoms had developed during the convalescence or after the patient had returned to duty. Some of these men were admitted from American camps and were in an earlier stage of convalescence than were the men returned from overseas. This may account, in part, for the lower average strength on admission than was found in the case of the men who broke down under strain. The gain in strength and the disappearance of the symptoms in graded exercises is about equally rapid in these two types. However, some complication may persist in the postinfection cases which limits their advancement in the graded work.

Patients giving a history of symptoms developing after acute rheumatic fever have not been included in this report of effort syndrome cases. The common incidence of rheumatic fever in organic heart disease influenced the separation of these cases into an independent group, even though a thorough study and close observation during a long period of graduated work failed to reveal any organic defect. In Tables 2 and 3 are appended the observations in thirty-three cases in which the men developed symptoms after acute rheumatic fever. It is shown that 88 per cent. of these men advanced into Grade 5 exercises, and 39.5 per cent. completed the highest (6) grade. In cases of the general postinfectious type, 90 per cent. of the men completed Grade 5, and 68 per cent. finished the work of all grades successfully. Men with arthritic symptoms are not included in this postrheumatic number, but among the postinfectious patients, a number had persisting complications. Arrhythmias due to some myocardial defect are more frequently found in the postrheumatic cases during the exercise work, and these men must be advanced in the grades only under the most careful observation.

#### GENERAL DISCUSSION

The classification used in this report is purposely broad, since the desire is to emphasize the fact that variations in type can occur among cases presenting the effort syndrome symptom complex rather than to advocate any fixed terminology. It is believed that a more rational understanding of this condition can be reached and a more successful treatment carried out when an appreciation of the variations in type is recognized and an individual study of each patient is made.

Men who have presented symptoms for a long period of time, and who have failed to stand up to their earlier military training, cannot be built up to a normal strength in the short time and by the intensive methods necessary during a military emergency. Such treatment will only increase the severity of the symptoms, and the patient is given a more fixed idea of invalidism in consequence. The treatment is more properly a civil problem, and should receive its deserved attention during the time of peace. The importance of recognizing this is emphasized when we consider the number of recruits who were found to be unfit for military service because of a poor physical development unassociated with any organic disease.

Men belonging to the type of chronic physical invalidism have a military value if they can be developed to a condition of greater strength and, what is even more important, they can be made fit to successfully undertake more active work in civil life with an improve-

ment in their economic life. There is an increase in their military value that is, to some degree, in direct proportion to their ability to stand up to more active civil work.

Men showing definite intelligence defect present the most discouraging problem in treatment. The mental sluggishness does not permit of a satisfactory cooperation from these men.

Where the symptoms have been of short duration and acquired during active military duty, the general strength shows a higher average and the men lose their general symptoms more rapidly. This is especially true where the condition follows the physical and nervous strain of front line fighting, and the symptoms are no more persistent than in the cases here reported. If comparisons are to be made, it must be remembered that our troops were not in the fighting line so long as were the allied forces. Also, the signing of the armistice removed any fear of a return to active duty which might have been an important factor in delaying recovery.

Men who develop the effort syndrome after acute infections will improve rapidly in strength and in symptoms through graded exercises. They may be limited in their advancement through the grades by some resulting complication. When carried out under proper supervision, well graded exercises should form an important part in the late treatment of infectious diseases.

No attempt has been made in this report to give the percentages of men returned to duty. It is doubtful if any reached the front line in time to take part in active fighting for a sufficient length of time to be a satisfactory test. A number have been heard from through personal communications, several months after they had returned to civil life, and these report having taken up more active work than had been their former occupations and having been free from symptoms.

All strength estimations included in this report were made with the assistance of Dr. John T. King, Jr., to whom I am indebted for most efficient cooperation. I wish to express my appreciation of the work done by the men who directed the classes in graded exercises: G. J. Altman, Paul M. Krimmel and Morris Kaufman. The general plan adopted for the exercises was worked out by these men and the success of the work was largely due to their able and faithful services.

## THE MARTIN STRENGTH TEST

### SPECIFICATIONS

*First.*—A self-registering spring balance and ice scale. A very satisfactory scale is now furnished by John Chatillon and Sons, 85 to 93 Cliff Street, New York City, as "Special Strength Tester. Style No. 100 B." The capacity should be designated in ordering and can be had in pounds (200) or kilograms (100).

*Second.*—An upright post with a hand hold. A stout post, 4 inches square and 6½ feet high, mounted on a firm base. The post should be smooth and have the corners rounded off. A strong rod, 1½ inches in diameter and 24 inches from the post, should be placed as a hand hold.

*Third.*—A stout table of ordinary height, not less than 6½ feet long and 2½ feet wide, with a cleat of wood about 2 feet by 1½ inches by 3 inches, securely fastened on the top of the table across one end, with the greater diameter vertical.

#### PROCEDURE

Ten groups of muscles are tested: 1. Right pectoral; 2. left pectoral; 3. right wrist flexors; 4. left wrist flexors; 5. right forearm flexors; 6. left forearm flexors; 7. right thigh adductors; 8. left thigh adductors; 9. right thigh abductors; 10. left thigh abductors.

After the loop of the balance is adjusted and the subject is in position, the command "hold back" is given. At this command the subject contracts the muscles of the group being tested with all his power and, simultaneously, the operator pulls on the spring balance. The tension must be developed as rapidly as possible, without jerking, and must be increased until the resistance of the subject is entirely overcome.

#### TECHNIC

**Pectoral Groups:** The subject stands at attention, with the middle of his back pressed firmly against the upright post, and the hand of the arm not being tested grasping the hand hold. The adjuster stands directly in front of the subject, facing him and places the loop of the balance about the arm to be tested, just above the elbow. With one hand he holds the loop in position and, grasping lightly the hand of the arm to be tested, draws the arm across in front of the subject's body as far as possible, keeping the arm straight and as close to the body as can be done and still give clearance for the loop. At the command "hold back," the subject makes all the resistance possible and the operator develops sufficient tension to draw the arm down to the side of the body. The pull must be discontinued before the arm has been drawn beyond the vertical line.

**Wrist Flexors:** The subject stands beside the upright post with the arm to be tested so flexed as to bring the forearm horizontal. The back of the forearm must rest against the post, and the hand project beyond the post to the ulnar process. The adjuster stands directly in front of the subject's palm. With one hand he holds the subject's wrist against the post and, with the other, he holds the loop in place. The loop is placed so that its middle is directly over the crease at the base of the fingers. Keeping the fingers straight, the subject's hand is flexed at the wrist. The operator pulls at an angle just less than 90 degrees from the plane of the subject's hand. Tension must stop as soon as the hand begins to yield.

**Forearm Flexors:** The subject lies on his back on the table, with his heels pressed firmly against the cleat. The adjuster stands at the subject's left for both flexors. His right hand holds the subject's forearm in a position of flexion, about 15 degrees toward the shoulder from the vertical, and places the loop about the wrist so that its upper edge is at the crease in the skin at the base of the hand. The operator stands at the foot of the table. Tension is relieved when the forearm reaches the vertical.

**Thigh Adductors:** The position of the subject is the same as for the forearm flexors, except that he presses against the cleat with only the foot of the leg that is not being tested. The adjuster stands at the foot of the table. With one hand he places the loop in the hollow just above the malleolus, seizes the subject's heel with the other hand, lifts the leg until the heel is just high enough to clear the other toe, and then draws the leg into extreme adduction. The toe of the leg to be tested must be upright. The operator stands at the side of the table, develops tension at the word of command and draws the leg outward from the side. Tension is relieved as soon as the leg has been drawn into line with the axis of the body.

Thigh Abductors: The positions of the subject and adjuster are the same as in the last test. The loop is adjusted as for the adductors but the pull is in the opposite direction. The leg is drawn out beyond the midline of the body to an angle of about 15 degrees, and the effort of the subject is to prevent the operator from drawing the leg into line with the body. The tension is relieved when the leg reaches the midline.

*Calculation.*—The sum of the strength shown by these ten groups of muscles constitutes in men 17.7 per cent. of the entire strength as found by this system of testing. To calculate the total strength therefor, the sum of these ten determinations must be multiplied by the reciprocal of 0.177, which is 5.65. The product thus obtained is the figure for the strength of the individual.

#### NOTE

This technic is printed with the consent of Dr. Ernest G. Martin, to whom I am indebted for permission to use the test. I wish also to express my appreciation of the suggestions regarding the technic that were given by Prof. F. S. Lee.

## EXPERIMENTAL EMPHYSEMA \*

SARAH R. KELMAN, M.D.

IOWA CITY

In the recent epidemic of influenza and bronchopneumonia, among the S. A. T. C. at the Iowa State University, there were about 1,100 cases with thirty-three fatalities. Of these, twenty came to necropsy.

One of the most striking and constantly present postmortem findings in these cases was a marked vesicular and interstitial emphysema. The vesicular emphysema was mainly marginal, but large emphysematous bullae were quite frequently observed subpleurally. The apices of both lungs, especially the upper lobes, were involved. In many cases superficial distended air vesicles ruptured and allowed an escape of air subpleurally, giving the lung a beaded appearance. The roots of the lungs were also quite commonly involved.

The interstitial emphysema involved mainly the anterior and posterior mediastinum, the layers of the pericardium and pericardial fat, the retroperitoneal and especially the perirenal tissues. The absence of inflammation and our inability to find organisms in stained preparations of these tissues, proved to us that the emphysema was not due to a gas bacillus infection. The interstitial emphysema was so uniformly present that we were at first inclined to consider it an artefact. But increased care in the handling and removal of the viscera, the absence of this phenomenon in cases that terminated fatally from causes other than influenza, and the location of the emphysema soon convinced us that this was not the case. The duration of illness in these cases varied from five to fourteen days, and the amount of lung involvement varied from a few bronchopneumonic patches with marked pulmonary edema to complete consolidation of all the lobes of both lungs, so that the vesicular emphysema could not be considered compensatory in nature in every case. Dyspnea and cyanosis were very prominent and constant symptoms, and in most cases altogether out of proportion to the amount of lung involvement.

These questions presented themselves:

1. How did air get into the mediastinal and retroperitoneal tissues?
2. What caused the unusual acute vesicular emphysema?

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\* From the Department of Pathology and Bacteriology, College of Medicine, University of Iowa.

\* Read before the Section on Pathology and Physiology at the Seventieth Annual Meeting of the American Medical Association, Atlantic City, N. J., June, 1919.

3. What was the cause of the marked dyspnea and cyanosis?

4. What relation, if any, was there between the dyspnea and cyanosis and the emphysema?

The object of the studies recorded in this paper was to reproduce experimentally (in laboratory animals, chiefly rabbits) the essential conditions obtained in the influenza cases and thus, perhaps, find an answer to these questions.

As there was no doubt in our minds that the emphysema in the interstitial tissues was due to an escape of atmospheric air from the lung, we performed the following experiments to determine the path by which such escape took place:

EXPERIMENT SERIES No. 1.—Rabbits were killed with ether. A tracheotomy was then performed and a glass tube connected by means of rubber tubing to a bicycle pump was ligated into the trachea. The pressure used varied from 10 to 15 mm. of mercury.

R1A was inflated by pumping six times in rapid succession. The abdomen became very tight and when opened there was an escape of air. The pumping was repeated and the path of the air observed. With each pumping the air could be seen to fill up the retroperitoneal tissues from above downward and then into the perirenal fat and thighs. The chest was then opened. The sternum was carefully removed causing as little disturbance as possible in the tissues of the anterior mediastinum, to prevent a break in their continuity. There was marked emphysema in the tissues of the anterior, superior and posterior mediastinum and about the loose areolar tissue of the pericardium. The lungs were markedly emphysematous, especially about the margins and at the roots. The chest cavity was then filled with normal salt solution and the pumping resumed. The air could then be observed escaping at the root of the lung in the vicinity of the great vessels and the pleural reflexion.

It is noteworthy that with the chest opened, no air could be forced down below the diaphragm. Presumably with the chest cavity opened the pressure was insufficient to force the air downward. Also a new path of least resistance was created with opening up the chest, namely, externally.

R2A, 3A and 4A were similarly treated, except that the number of insufflations was increased and the interval between decreased. The results were the same as for R1A because a limit is reached beyond which increased pumping produces no further change.

An attempt to photograph some of these animals illustrating the emphysema, proved unsuccessful because of high lights and numerous other technicalities. Most of the air escaped as soon as the continuity of tissues was broken and an avenue of escape thus afforded. Being anxious to secure a photograph we tried out another procedure.

R9A was killed and tracheotomized in the same way. Its abdomen was then opened and the entire animal immersed in 10 per cent. liquor formaldehydi; then he was pumped continually for an hour and fifteen minutes. Our object was to secure fixation of the tissues before the air had a chance to escape. We then opened the chest enough to allow the liquor formaldehydi to enter in order to secure fixation of the thoracic viscera. The animal remained in this solution for two days.

The result was somewhat disappointing, for while there was some emphysema about the great vessels, especially in the region of the kidneys and in the thighs, the amount was negligible as compared with what had been

obtained in the previous animals. The explanation here is probably the same as given for the animal with the opened chest, namely, insufficient pressure, the abdomen having been opened.

Before discussing the route taken by the air in reaching the interstitial tissues, it might be well to review the anatomy of the reflexions of the pleura and pericardium.<sup>1</sup>

The constituent parts of the root of the lung are (1) the two pulmonary veins, (2) the pulmonary artery, (3) the bronchus and (4) one or more small bronchial arteries and veins, the pulmonary lymph vessels and some bronchial glands. Above the root of the lung the

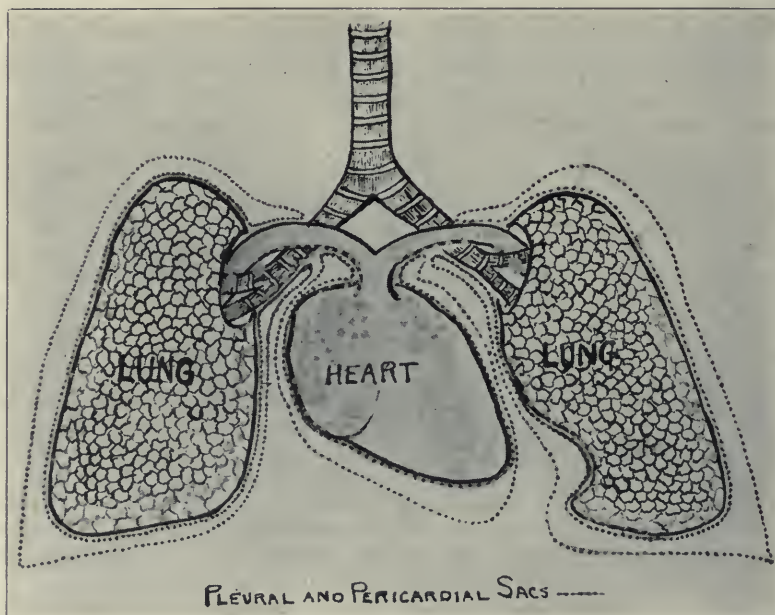


Fig. 1.—Relation of pleura, pericardium and blood vessels illustrating the direct path of the early interstitial emphysema in pericardial fat tissue.

left mediastinal pleura is applied to the arch of the aorta and the phrenic and vagus nerves, to the left innominate veins, to the left superior intercostal vein and the left common carotid and subclavian arteries, to the esophagus and thoracic duct. The right mediastinal pleura, on the other hand, is applied above the root of the lung to the superior part of the vena cava superior and to the right innominate vein, to the innominate artery, to the vena azygos, as it hooks forward above the bronchus, to the vagus and phrenic nerves and to the right side of the trachea. The fibrous pericardium at its apex and posteriorly is gradually lost on the great vessels which enter and emerge

1. Cunningham's Anatomy.

from the heart, giving sheaths to the aorta, the two branches of the pulmonary artery, the superior vena cava, the four pulmonary veins and the ligamentum arteriosum.

This review will aid in mapping our route.

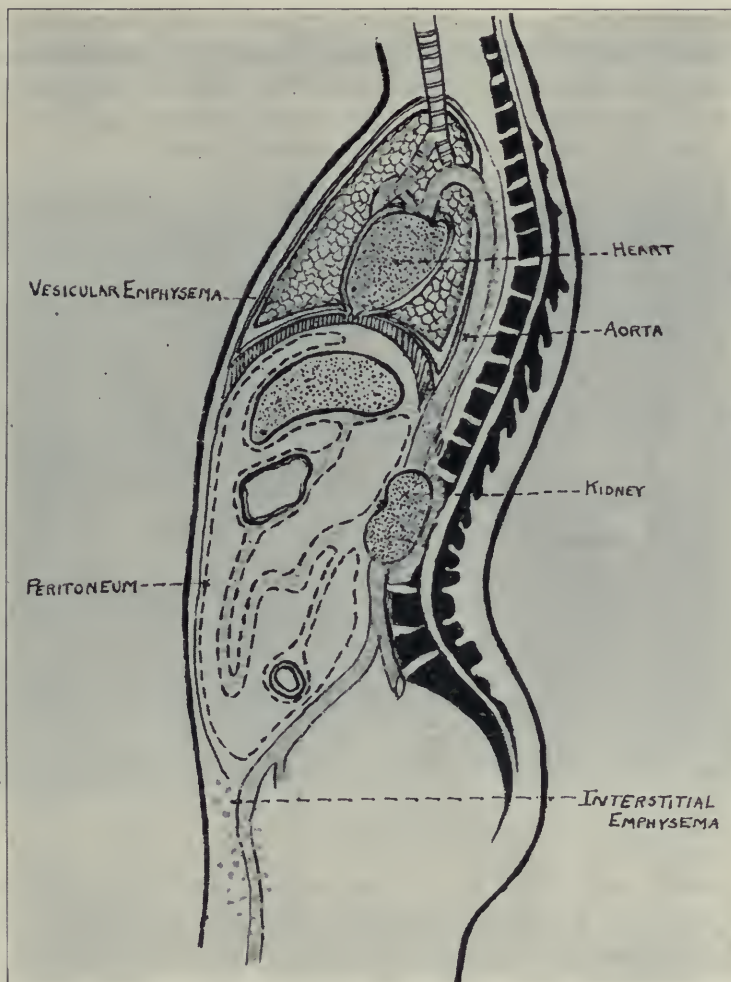


Fig. 2.—Emphysematous paths in relation to the pleurae, pericardium and peritoneum.

First, a vesicular emphysema is produced. Increased intrapulmonary pressure causes rupture of some of the superficial distended air vesicles and there is an escape of air underneath the visceral pleura, which is rather firm. The air finds less resistance in escaping underneath the pleura toward the hilus than to break through it. From the

hilus it travels along the pleural reflexions over the pulmonary arteries and veins to where it meets the pericardial reflexions over the same vessels (Figs. 1 and 2) the tissues of the anterior mediastinum, especially the pericardium and pericardial fat, thence it extends to the superior mediastinum and following the course of the great vessels enters the posterior mediastinum and passes downward into the retro-peritoneal tissues—the perirenal tissues being most commonly invaded; it then enters the folds of the omentum, the region of the great vessels and downward into the thighs. Superiorly, some of the air follows the subclavian vessels and enters the axillary space.



Fig. 3.—Rabbit 10 A. Acute vesicular emphysema following artificial convulsions. Killed forty-eight hours later.

Berkley and Coffen<sup>2</sup> report nine cases of extensive subcutaneous emphysema and spontaneous pneumothorax as a complication of influenzal bronchopneumonia. In their cases the emphysema involved the supraclavicular and infraclavicular spaces, neck, face, arms, chest, trunk, genitalia and thigh. They discuss two possible routes, the intrapleural and the extrapleural. They state that in order for air to pass from the lungs to the chest wall by the intrapleural route, it must pass through both visceral and parietal pleura. To do so, without producing a pneumothorax, it must be assumed that adhesions existed

2. Berkley, Hugh K., and Coffen, T. Homer: Generalized Interstitial Emphysema and Spontaneous Pneumothorax as Complications of Bronchopneumonia, *J. A. M. A.* **72**:535 (Feb. 22) 1919.

between these membranes at some area, and that the passage of air occurs at this point. At necropsy this seemed the possible route in only one of their cases. They then came to the conclusion that the extrapleural route, as we explained above, is the route taken.

In our experimental cases the intrapleural route is entirely out of the question, as there were no adhesions found at any time. Symmers<sup>3</sup> in discussing the acute vesicular emphysema in post influenzal bronchopneumonia reports three cases of interstitial emphysema. In two cases the soft tissues of the supraclavicular spaces were crepitant with infil-



Fig. 4.—Rabbit 5 A. Interstitial emphysema in the tissues of the anterior mediastinum following artificially produced convulsions. Killed thirty minutes after last convulsion.

trated air; in another case the soft tissues of the posterior aspect of the mediastinum were permeated by myriads of emphysematous bullae varying in size from the head of a pin to that of a small marble, air extended thence into the soft tissues of the precordial area downward to the pericardial attachment to the central tendon of the diaphragm, forward into the retrosternal region and thence through the upper apertures of the thorax into the neck and lower portions of the face, downward into the subcutaneous tissues as far as the crest of the

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3. Symmers, Douglass: The Pathologic Similarity of the Pneumonia of Bubonic Plague and Pandemic Influenza, *J. A. M. A.* **71**:1482 (Nov. 2) 1918.

ilium and the lower level of the costal slope on the right. However, he assumes that the interstitial emphysema was due in the first two instances to a rupture of an emphysematous bulla near the apex of the lungs, thus taking the intrapleural route; in the third case the assumption is that an emphysematous bulla ruptured near the root of the lung. In neither case does he mention the presence of any adhesions, nor was he able to find the point of rupture at the necropsy. In his fourth case there was a spontaneous pneumothorax, which was most likely caused by a rupture of a distended vesicle, the air breaking through the visceral pleura.

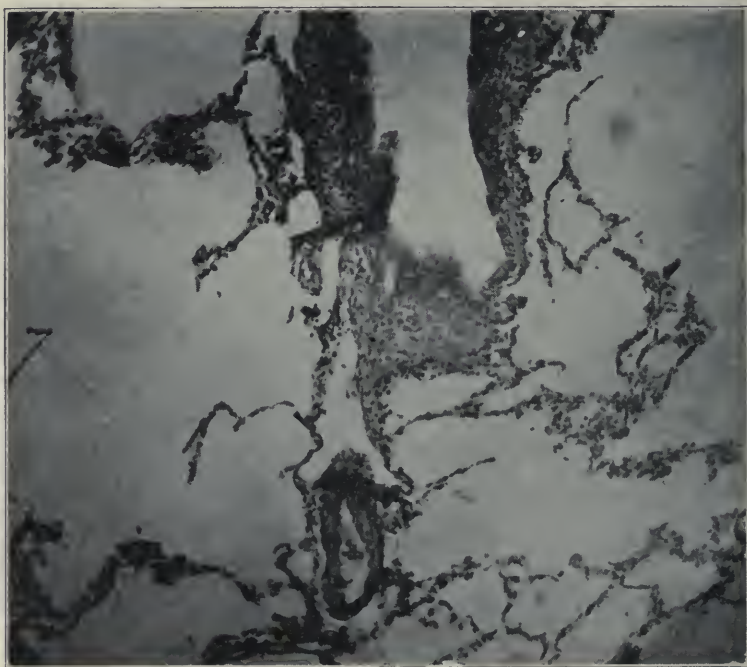


Fig. 5.—Rabbit 5 A. Acute vesicular emphysema.

In our experimental cases we were at no time able to produce an emphysema above the clavicles. This may be explained in two ways—either by a difference in the anatomy between the human and the rabbit, or by a break in continuity of tissues due to the tracheotomy wound.

EXPERIMENTAL SERIES No. 2 had for its object the production of artificial emphysema in living animals and observing its effect on them.

A catheter was connected with a bellows; this catheter was inserted into the trachea and the bellows pumped in such a way as to produce a definite number of respirations per minute, to imitate convulsions, varying in number, as nearly as possible, each convulsion consisting of three respiratory seizures (Table 1).

TABLE 1.—RESULTS OF ATTEMPTS TO PRODUCE ARTIFICIAL EMPHYSEMA IN LIVING ANIMALS

Number	No. Respirations and Time	Respiration per Min.	Seizures in Each Series	Interval between Each Seizure	No. of Series	Interval between Series	Pressure	Remarks
5A	25 in 20 sec.	75	3	30 sec.	1	.....	8-12 mm. Hg.	Four minutes after last artificial respiration, respirations are fifty-eight per minute, deep and labored; ears show cyanosis. Killed thirty minutes after last convulsion. Marginal emphysema; interstitial emphysema in anterior and superior mediastinum and about the pericardium
6A	25 in 20 sec.	75	3	15 sec. first series, 30 sec. second two series	3	7 min. 5 min.	8-12 mm. Hg.	Twenty minutes after last inflation the respirations are irregular, Cheyne-Stokes in character, 128 per minutes. Cyanosis of ears, mouth and about eyes. Ten minutes later respirations are 108, otherwise condition as above. Animal seems very thirsty. Forty minutes later killed. Marked marginal vesicular emphysema; interstitial emphysema in anterior and posterior mediastinum, about the pericardium in the perirenal tissues in the left side, in the retroperitoneal tissues, along the aorta on the right side, same in the omentum
7A	25 in 20 sec.	75	3	30 sec.	7	5 min.	2 mm.	Respirations were jerky ten minutes after convulsions. Killed twenty minutes after last convulsion. Marginal emphysema, interstitial emphysema about the pericardium
8A	25 in 20 sec.	75	3	30 sec.	7	5 min.	2 mm.	Between intervals the respirations varied from 58 to 115, were quite irregular and jerky, Cheyne-Stokes; sometimes stertorous in character; cyanosis. Killed twenty minutes after last artificial respiration. Marked marginal vesicular emphysema. No interstitial emphysema.
10A	25 in 20 sec.	75	3	30 sec.	3	5 min.	2 mm.	Two hours after last convulsion, marked cyanosis, irregular respirations. Killed forty-eight hours later with one blow so as to avoid a struggle. Emphysema very marked on the margins and at root of lung; some interstitial emphysema about pericardium, otherwise lungs are normal
11A	25 in 20 sec.	75	3	30 sec.	3	5 min.	2 mm.	Respirations between seizures irregular, jerky and Cheyne-Stokes in character. Cyanosis. The animal apparently completely recovered in twenty-four hours. Killed five days later by a single blow to avoid a struggle. Very slight marginal emphysema
12A	25 in 20 sec.	75	3	30 sec.	3	5 min.	2 mm.	Symptoms as above. Animal completely recovered in twenty-four hours. Killed six days later. Only very slight marginal emphysema

From Table 1 it will be observed that acute vesicular emphysema can be induced by artificial means (Figs. 3 and 4), that such an emphysema in itself is sufficient to produce dyspnea and cyanosis. According to Torrey and Grosh<sup>4</sup> the pulmonary emphysema interferes with the mass movement of the venous blood thus producing dyspnea and cyanosis.

It will also be noticed that the amount of interstitial emphysema was entirely dependent on the pressure used (Fig. 5). Where a

4. Torrey, Robert G., and Grosh, Lawrence C.: Acute Pulmonary Emphysema Observed During the Epidemic of Influenzal Pneumonia at Camp Hancock, Am. J. M. Sc. **157**:170 (Feb.) 1919.

pressure of from 8 to 12 mm. of mercury was used, the air was forced into the mediastinal and retroperitoneal tissues. On the other hand, where the pressure was only 2 mm. of mercury, two or three times the number of so-called convulsions was not sufficient to force much air into the interstitial tissues.

The factors producing the emphysema having been removed the animal recovers within a short time, the air being almost completely absorbed in from six to eight days (Fig. 6).

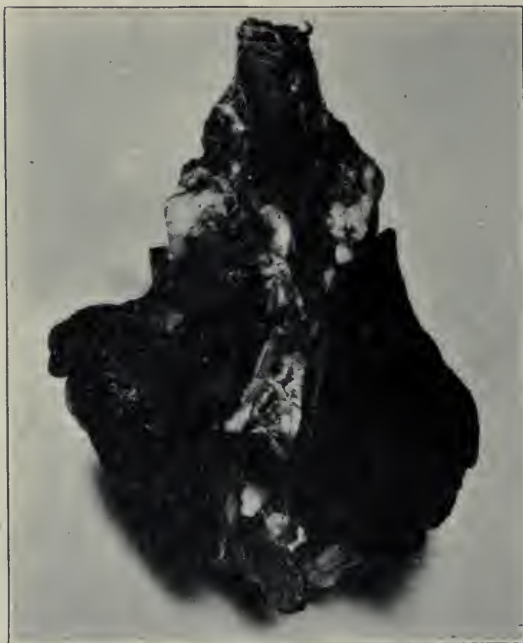


Fig. 6.—Rabbit 11 A shows almost complete disappearance of the emphysema six days after artificial convulsions were produced.

EXPERIMENT SERIES No. 3.—In the above experiment we found that emphysema will produce respiratory distress (dyspnea and cyanosis). Next we attempted to produce respiratory distress to determine if it in turn will produce emphysema.

R 13 A was sensitized with 0.001 c.c. of egg white. Seventeen days later  $1\frac{1}{2}$  c.c. of egg white was injected intravenously. The animal had a violent convulsion two minutes after the injection, another one five minutes later and died in convulsions ten minutes after injection.

The postmortem findings were some marginal emphysema and a small amount of interstitial emphysema about the pericardium and at the root of the lungs (Figs. 7 and 8).

R 14 A was sensitized with  $\frac{1}{2}$  c.c. of sheep serum. Seventeen days later 2 c.c. of sheep serum were injected intravenously. Three minutes after



Fig. 7.—Rabbit 13 A. Acute vesicular emphysema following an anaphylactic shock.

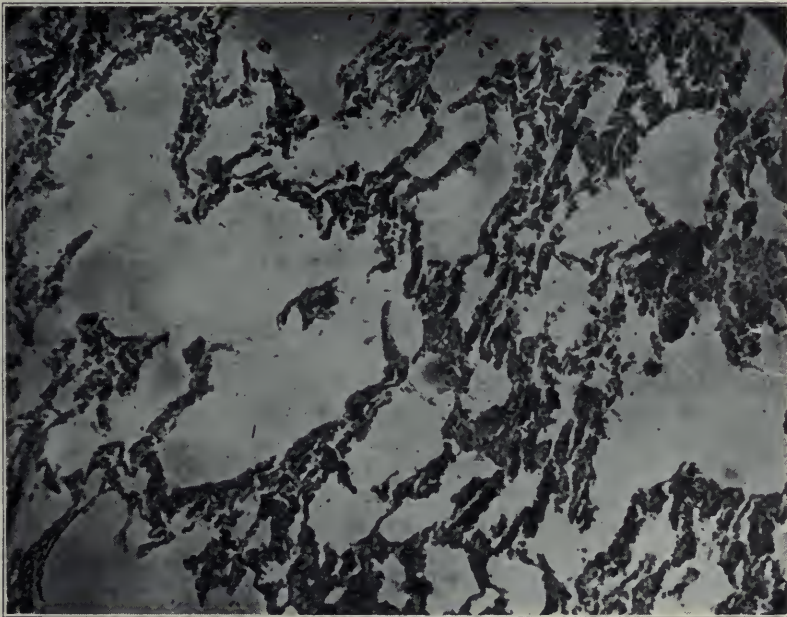


Fig. 8.—A microscopic section from Rabbit 13 A.  $\times 85$ .

injection the animal cried out as if in great distress; this was followed by a violent convulsion. Eight minutes after injection the animal was dead. The postmortem findings were marked marginal vesicular emphysema, interstitial emphysema in the posterior mediastinum and in the pericardial areolar tissues.

R 15 A was treated the same as R 14 A. This animal had a violent convulsion five minutes after and died eight minutes after injection. Postmortem findings were the same as for R 14 A.

Thus respiratory distress caused by anaphylaxis will produce emphysema. It is fair to assume that respiratory distress from any cause will operate in the same way. Acute vesicular emphysema, on

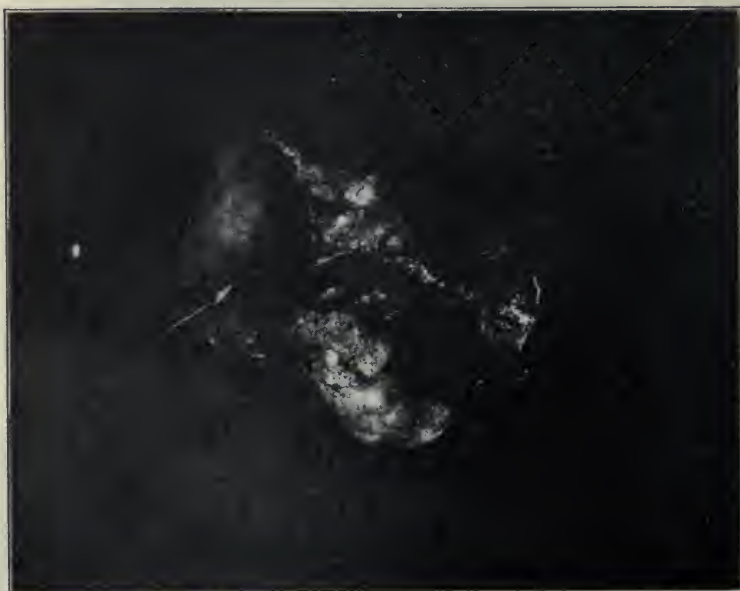


Fig. 9.—Rabbit 23. Vesicular emphysema following injection with influenza toxin.

the other hand, will cause respiratory distress, in a way, producing a vicious circle.

EXPERIMENTAL SERIES No. 4.—Our last set of experiments consisted in inoculating animals with given amounts of broth cultures of *B. influenzae* (Pfeiffer) or the filtrate of broth cultures.

Out of eighteen rabbits necropsied, fifteen showed varying degrees of vesicular and interstitial emphysema (Figs. 9, 10 and 11). Every one of the animals died in convulsions and marked respiratory distress (Table 2).

Oleate hemoglobin broth, described by Avery<sup>5</sup> as a good culture medium for *B. influenzae*, was used in every case.

5. Avery, O. T.: A Selective Medium for *B. influenzae*—Oleate Hemoglobin Agar, J. A. M. A. **71**:2050 (Dec. 2) 1918.

TABLE 2.—RESULTS OF INOCULATION WITH *BACILLUS INFLUENZAE* (PFEIFFER)

No.	Material Injected	Death after Injections	Postmortem Findings
R7	4 c.c. of influenza toxin	1 hr. and 20 min.	Congestion of lungs, marked marginal vesicular emphysema. Interstitial emphysema in tissues of anterior mediastinum, especially about pericardium
R10	7 c.c. of influenza toxin	1 hr. and 30 min.	Marked vesicular emphysema
R11	3 c.c. oleate hemoglobin broth culture	1 hr. and 40 min.	Some vesicular emphysema
R13	2 c.c. oleate hemoglobin broth culture	3 hours	Vesicular emphysema and interstitial emphysema between layers of pericardium
R12	5 c.c. oleate hemoglobin broth culture	5½ days	Lungs markedly congested, some vesicular emphysema, some interstitial emphysema about the pericardium
R5	2 c.c. oleate hemoglobin broth culture	12 hours	All lobes of both lungs were markedly congested. Marginal vesicular emphysema and some interstitial emphysema about the pericardium
R18	4 c.c. oleate hemoglobin broth culture	20 days	(This animal died with symptoms of meningitis.) Lungs perfectly normal except for very marked marginal vesicular emphysema
R19	5 c.c. oleate hemoglobin broth culture	5½ days	Lungs slightly congested, marked marginal vesicular emphysema
R21	3 c.c. filtrate	5 weeks	Small pneumonic patches in both lungs. Vesicular emphysema at the margins and at the root of the lungs. Considerable interstitial emphysema in the anterior mediastinum and in the retroperitoneal tissues along the great vessels
R23	4 c.c. filtrate	11 days	Lower lobes of both lungs congested. Marked vesicular emphysema. Some emphysema in the tissues of the anterior mediastinum
R25	2 c.c. oleate hemoglobin broth culture	36 hours	Vesicular emphysema along the margins and root of lungs. Some interstitial emphysema in the mediastinal and retroperitoneal tissues
R27	2 c.c. oleate hemoglobin broth culture 24 hours later 5 c.c. oleate hemoglobin broth culture	29 hours after first injection	Hemorrhagic spots varying from 1 to 3 cm. in diameter are present throughout both lungs. Marginal vesicular emphysema was present in all lobes of both lungs. Some interstitial emphysema in anterior mediastinum about the pericardium
R28	5 c.c. salt solution suspension	29 hours	Lungs grossly normal except some marginal vesicular emphysema and some interstitial emphysema in the tissues about the pericardium
R29	5 c.c. salt suspension	10 hours	Lungs slightly congested. Some marginal vesicular emphysema and some emphysema in anterior mediastinal tissue
R30	5 c.c. oleate hemoglobin broth culture	10 hours	Marked congestion of posterior aspects of both lungs. Vesicular marginal emphysema

From Tables 1 and 2 it will be seen that emphysema, both vesicular and interstitial, is constantly found postmortem in animals dying after an injection of the *B. influenzae* or its toxin, irrespective of the duration of the illness or the amount of lung involvement.

We have shown in previous experiments that convulsions alone will produce acute vesicular emphysema by producing respiratory distress. But it may be pointed out that respiratory distress alone will not produce the marked emphysema seen in postinfluenzal bronchopneumonia as is shown by pneumonia due to other organisms, where the respiratory distress is apparently just as great. At first glance it would appear that we would have to seek an explanation elsewhere.

Torrey and Grosh<sup>4</sup> found in their cases a destructive softening in the lung parenchyma. Alexander and Follet,<sup>6</sup> in discussing generalized

6. Alexander, M. E., and Follet, E. C.: Subcutaneous Emphysema with the Report of Several Cases, Particularly One with Very Extensive Generalized Emphysema, J. A. M. A. 72:930 (March 29) 1919.

emphysema in infants, assume that the emphysema is produced by rupture of some of the pulmonary vesicles by a violent exertion or coughing fit, this rupture being due to a congenital weakness of the lung parenchyma. LeCount,<sup>7</sup> after an exhaustive study of microscopic sections of postinfluenzal bronchopneumonic lung, finds marked disseminated necrosis of the alveolar lining as well as of the alveolar capillaries.

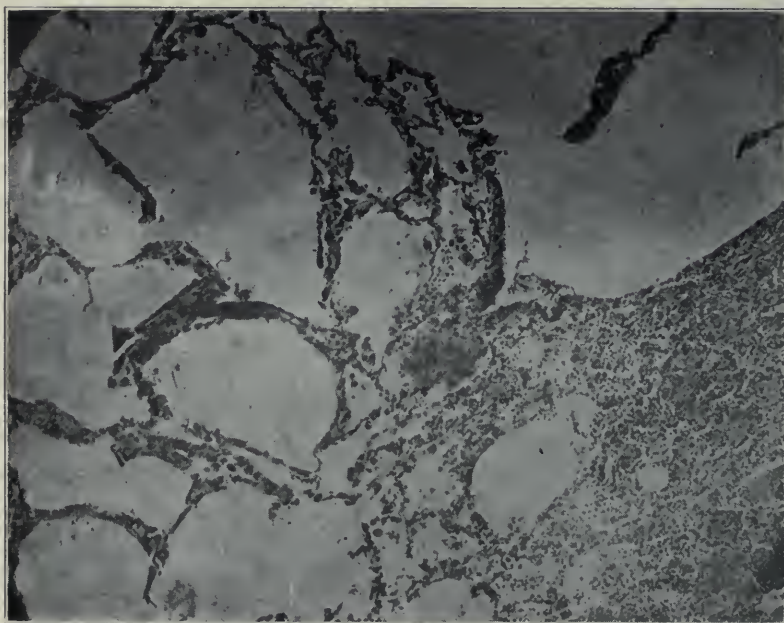


Fig. 10.—Rabbit 19. Showing a bronchopneumonic patch and vesicular emphysema five and a half days after injection with oleate hemoglobin broth culture of *B. influenzae*.  $\times 450$ .

The evidence cited may account for the discrepancy. However, the time element must be considered. The respiratory distress in lobar pneumonia or bronchopneumonia from other causes, appears comparatively late, when a considerable amount of lung has been thrown out of function, whereas in influenzal infection, dyspnea and cyanosis are almost coincident with the onset of the disease.

One more point must be brought out. The vesicular emphysema is invariably superficial, either on the margins where the lung is very thin, about the root of the lungs, superficially at the apices, or anywhere on the anterior aspect of the lungs superficially. This brings in the mechanical factor. The lung alveoli that are placed centrally,

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7. LeCount, E. R.: Disseminated Necrosis of the Pulmonary Capillaries in Influenzal Pneumonia, J. A. M. A. **72**:1519 (May 24) 1919.

are prevented from stretching beyond their limit of elasticity by the surrounding lung tissue; the alveoli more superficially placed lack that support, hence, are the first ones to suffer.

The following explanation seems plausible and fits in with our experimental work. The toxin of the infecting organism or virus, whatever that may be, exerts an irritating influence on the respiratory center, inducing a dyspnea. This assumption is further strengthened

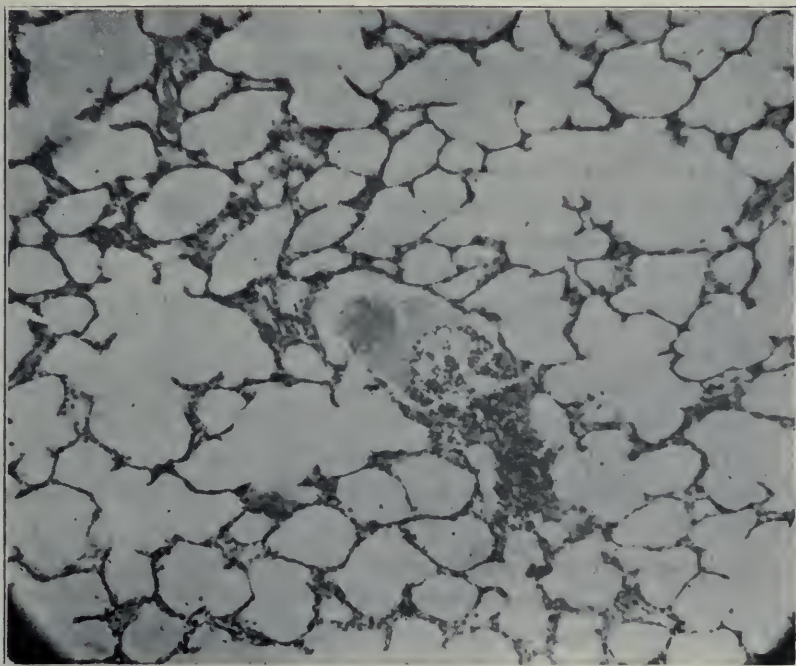


Fig. 11.—Same as Figure 10; more emphysema.  $\times 85$ .

by the fact that in the epidemic of influenza the pulse was comparatively slow, indicating a possible irritation of the vagus centers, in other words, irritation of the basal ganglia. Dyspnea, as we have shown above, is sufficient in itself to produce emphysema. It is reasonable to suppose that the virus which exerts a toxic action on the respiratory center, also acts locally. Whether the action is due to loss of tone, destruction of lung parenchyma, as pointed out by Torrey and Grosh,<sup>4</sup> or a destruction of the lining of the alveoli, as pointed out by LeCount,<sup>7</sup> is difficult to say. There is no doubt that such action, however it operates, causes a marked weakening of the alveoli.

Respiratory distress on top of weakened alveoli will greatly augment the emphysema. We demonstrated the fact that emphysema in itself will produce respiratory distress and cyanosis. Experimentally,

as soon as the cause is removed, the emphysema disappears in from six to eight days, but in an influenzal infection a vicious circle is established.

#### CONCLUSIONS

1. Interstitial emphysema as found in our experiments and in fatal cases of postinfluenzal bronchopneumonia is a result of escape of air from the lungs, preceded by a marked vesicular emphysema.

2. The path taken by air escaping from the lung into the tissues is by way of the root, following the reflexion of the pleura and pericardium along the great vessels.

3. Marginal vesicular emphysema can be induced artificially by inducing respiratory distress.

4. Marginal vesicular emphysema as found by our experiments, is a mechanical process due to insufficient support of the marginal alveoli and initiated by respiratory distress.

5. Emphysema in itself is capable of producing dyspnea and cyanosis.

6. Emphysema, both interstitial and vesicular will disappear in from six to eight days after the cause is removed.

7. Acute vesicular emphysema found in fatal cases of postinfluenzal pneumonia is probably due to a combination of causes each intensifying the other.

- (a). A toxic action of the virus on the lung parenchyma, causing a marked weakening of the alveoli.
- (b). A toxic action of the virus on the respiratory center producing dyspnea and cyanosis, which in itself is sufficient to produce emphysema.
- (c). The emphysema thus produced in its turn, increasing the dyspnea and cyanosis.
- (d). The above factors combined acting on already weakened alveoli produce the acute vesicular emphysema observed in postinfluenzal bronchopneumonia.

We desire to acknowledge our indebtedness to Dr. Henry Albert, our chief, for very valuable suggestions, and to Dr. Henrietta Calhoun of the department staff, for material aid in handling the animals, assisting with photographs and making the diagrams, and also to Mr. J. Anderson, the department technician, who made all the photographs.

A PRELIMINARY SURVEY OF THE THYROID GLAND  
AMONG TWO THOUSAND ONE HUNDRED AND  
EIGHTY-TWO RECRUITS AT CAMP  
LEWIS, WASHINGTON

WILLIAM J. KERR, M.D.

Major, M. C., U. S. Army; Chief of the Medical Service, U. S. Army Base  
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SAN FRANCISCO

INTRODUCTION

The following survey is based on the examination of 21,182 recruits of the second draft arriving at Camp Lewis, Washington, in April and May, 1918. The survey was taken to determine the number of recruits showing enlargement of the thyroid at the time of induction into the service, and to provide a record in such cases so that changes taking place during training could be more accurately estimated. In addition to making observations as to the size and portions of the thyroid, the occurrence of certain signs and symptoms supposed to be associated with thyroid disease were also noted. The age of the individual, occupation, residence and family history of goiter were noted. These with the objective findings mentioned above form the basis of the report, and will be taken up under their appropriate headings.

In making this survey it was hoped that the data would form a basis to determine the fitness of recruits with thyroid enlargement for general military service, and furthermore whether any particular group of cases withstood the rigor of training better than others. Incidentally, the survey has afforded an opportunity to study the geographic distribution of endemic goiter in a large area of the United States.

My attention was first particularly called to the question of thyroid disease in the army during the fall and winter of 1917 and 1918 when the soldiers were undergoing intensive training. At that time very few cases of organic heart disease were being referred to the cardiovascular examiner but a large proportion of the referred cases presented rather significant functional disorders or many of the signs and symptoms of the syndrome described by Dr. Thomas Lewis under the term "Neurocirculatory asthenia." The frequency of thyroid enlargement in these cases was also noted, and it seemed that the frequent association was too common to lack significance. In these

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\* President of the cardiovascular board when the survey was made.

cases the enlargement of the thyroid was not marked and had, therefore, not attracted particular attention at the time of mustering into service, thus without a record of the condition at the time of induction into the service, no estimate of the changes taking place under training could be made.

The examinations were made within the first few days after the recruits reported at camp, at the time when the examinations were made by the special examining boards. One of the cardiovascular examiners was detailed for this duty. I wish to express my appreciation to Lieut. Carl P. Moran, M. R. C., who assisted in making the examinations, but who was ordered elsewhere before the survey was completed, and to contract surgeon Thomas Addis for his assistance throughout. A uniform method for the examination was adopted. The subjects, stripped to the waist, passed by in single file. If there was no obvious enlargement of the thyroid gland on swallowing, the examiner placed a thumb on each side of the neck just below the cricoid cartilage and the subject was asked to swallow again. By this latter method definite enlargements were often noted which were not revealed by inspection. Following the examination of the thyroid gland the presence or absence of eye signs, tremor, tachycardia, vaso-motor instability, moist skin, curved nails and clubbing of the fingers were noted. The findings were dictated to a clerk who passed the subject on to another clerk who completed the record of name, age, residence, occupation, family history of goiter, etc., as per attached form.

## PRELIMINARY GOITER STUDY

Drafted from: Town:		County:		Date:.....1918	
Name		Rank		Co. State:	
Age		Occupation		Regiment: Wages	
Residence the past year:		Birthplace:		Sister Brother	
Family history of goiter:		Father Mother		Sister Brother	

## SYMPTOMS

Dyspnoea	Nervousness	Loss in weight
Weakness	Headache	Diarrhoea
Palpitation	Dizziness	Constipation
Pain around heart	Apprehension	Polyuria
Sweating	Insomnia	
When goiter appeared	Changes in size	Pressure symptoms

## FINDINGS

Type of individual:	Asthenic	Normal	Sthenic
Size of thyroid	Small	Moderate	Large
Character of tumor:	Soft	Hard	Nodular
Portion involved: Isthmus	Right lobe	Left lobe	Diffuse
Tremor:	Vaso-motor instability		
Eye signs	Heart findings		
Clubbing of Fingers	Curved nails		
Pulse rate:	Mottling of skin		
Diagnosis:	Accept	Domestic service only	Reject

TOTAL NUMBER AND PERCENTAGE OF RECRUITS WITH  
ENLARGED THYROIDS

Among 21,182 recruits, 4,693, or 21 per cent., were found to have "enlarged thyroids."

In considering these figures it is important to bear in mind our definition of what constituted thyroid enlargement. Any man in whom the gland or any part of it could be felt distinctly on swallowing was classed as having an enlarged thyroid. This definition was, of course, recognized as being an altogether arbitrary one. It was adopted because for our statistical purposes it seemed essential to have a sharply defined standard. But it is clear that our total figures must include many cases in which the limits of the physiologic variation in the size of the thyroid were not exceeded, and which were classed as instances of enlargement because a thin neck or poorly developed muscles made it easier than usual to feel the gland. On this account the classification of these cases according to the degree of enlargement in subsection A is of particular significance.

TABLE 1.—THE NUMBER AND PERCENTAGE OF LARGE OR MODERATELY ENLARGED AND OF SMALL THYROIDS IN 4,693 CASES OF ENLARGED THYROIDS FOUND IN 21,182 RECRUITS

Size	Number	Percentage
Large and moderately enlarged.....	1,276	27
Small.....	3,417	73

*Degree of Enlargement.*—In Table 1 it is shown that of the 4,693 cases of "enlarged thyroids," 27 per cent. were classed as moderately or greatly enlarged, and 73 per cent. as instances of a small degree of enlargement. The smaller class includes only cases in which the thyroid enlargement was so manifest that no element of judgment entered into its recognition. This, then, was a uniform group of cases clearly marked off by the existence of a striking anatomic abnormality. On the other hand, the larger class is composed of a mixture of cases in which there was almost certainly an increase in the size of the thyroid and of cases in which there was almost certainly no enlargement. While in the first group the enlargement was certain, in the second there was a variation through all degrees between a high degree of probability to a bare possibility of enlargement.

By restricting attention only to those cases in which the enlargement was certain the true incidence of endemic goiter is doubtless greatly underestimated, yet even so the number of such cases (1,276) is surprisingly high and constitutes nearly 6 per cent. of the total number of recruits examined.

TABLE 2.—THE PART OF THE THYROID GLAND IN WHICH ENLARGEMENT WAS NOTED

Location	Number	Percentage
Diffuse .....	1,776	38
Isthmus .....	2,417	52
Right lobe .....	259	5
Left lobe .....	192	4

Table 2 shows that in 38 per cent. of the cases the enlargement was noted as diffuse, in 5 per cent. as being mainly or entirely an enlargement of the right lobe and in 4 per cent. of the left lobe. The remainder, or 52 per cent. of all the cases, are given as enlargements of the isthmus. The large proportion of isthmus cases is of course due to the fact that in the lesser degrees of enlargement, it was only the isthmus which could be felt. In most of these cases the probability is that the enlargement was more or less uniform in all parts of the gland.

*C. Distribution of Goiter in the Families of Recruits with Thyroid Enlargement.*—Table 3 gives the percentage of goiters in the members of the families of the recruits with thyroid enlargement. These data were compiled from the statements of the recruits.

TABLE 3.—DISTRIBUTION OF GOITER IN THE FAMILIES OF 4,693 RECRUITS WITH THYROID ENLARGEMENT AS OBTAINED FROM THEIR HISTORIES

Members of Family	Number	Percentage
Sisters .....	554	52
Mothers .....	311	29
Brothers .....	172	16
Fathers .....	33	3

Among the four categories of this table, a comparison is possible between the percentage of sisters and brothers affected, since the total numbers of sisters and brothers were probably approximately the same. The figures show that there were more than three times more sisters than brothers affected. Similarly, a comparison may be drawn between the incidence of goiter in mothers and in fathers. Here the difference is still more marked, 311 mothers as opposed to only thirty-three fathers with goiter. These cases probably include only cases in which the goiter was particularly prominent, for most of the men came from districts where endemic goiter is so prevalent, that minor degrees of enlargement are apt to be considered as within the range of normality.

*D. Age Distribution in Recruits with Thyroid Enlargement.*—In making the survey the age of individuals with enlargement of the thyroid gland was noted in 4,290 cases out of 4,693 recruits with enlarged thyroids. The number of cases by years and percentage by years is recorded in Table 4.

TABLE 4.—NUMBER OF CASES BY YEARS OF AGE  
No. of Enlarged

Age	Thyroids	Per Cent.
21.....	33	0.8
22.....	622	14.5
23.....	680	15.85
24.....	550	12.8
25.....	479	11.2
26.....	432	10.1
27.....	383	8.9
28.....	335	7.8
29.....	323	7.5
30.....	208	4.85
31 and 32.....	245	5.7
Total .....	4,290	100.0

The figures show that there were very few cases in the twenty-first year. This is due to the fact that in April and May, 1918, when the recruits were inducted into the service there were very few men of the 1917 registration who had not reached their twenty-second birthday. The figures for thirty-one years are larger than for the thirtieth year because it includes all men who were 31 years of age and those who had passed their thirty-first birthday when they were inducted into the service. The largest number of enlarged thyroids was noted in men 23 years of age. The lower figure for those of 22 years of age is possibly caused by an increased voluntary enlistment of men under their twenty-third year.

In order to determine whether the decrease in the percentage of thyroids after the twenty-third year is apparent or real, the records of 2,000 unselected recruits were reviewed. The number and percentage of men from 21 to 31 years of age are recorded in Table 5.

TABLE 5.—NUMBER OF MEN AT VARIOUS AGES  
No. of Recruits

Age	In Given Age	Per Cent.
21.....	15	0.75
22.....	268	13.4
23.....	287	14.35
24.....	252	12.6
25.....	222	11.1
26.....	200	10.0
27.....	167	8.35
28.....	190	9.5
29.....	158	7.9
30.....	108	5.4
31.....	133	6.65
Total.....	2,000	100.0

A comparison of the above percentages with those for enlarged thyroids with ages shows that the decrease in the number of thyroids from 21 to 31 years of age is only apparent. It appears definitely shown that there is no decrease in the number of cases of thyroid enlargement between 21 and 31 years of age. The following curve illustrates the point better.

*E. The Incidence of Certain Abnormal Physical Signs in Individuals with Thyroid Enlargement.*—Statistical data were collected on the frequency of certain signs in cases of goiter. The selection for study of the particular signs defined below was based on the previous experience of the Board in the examination of cases of thyroid enlargement referred to it on account of various complaints or defects. This experience had given rise to a seemingly well founded impression that

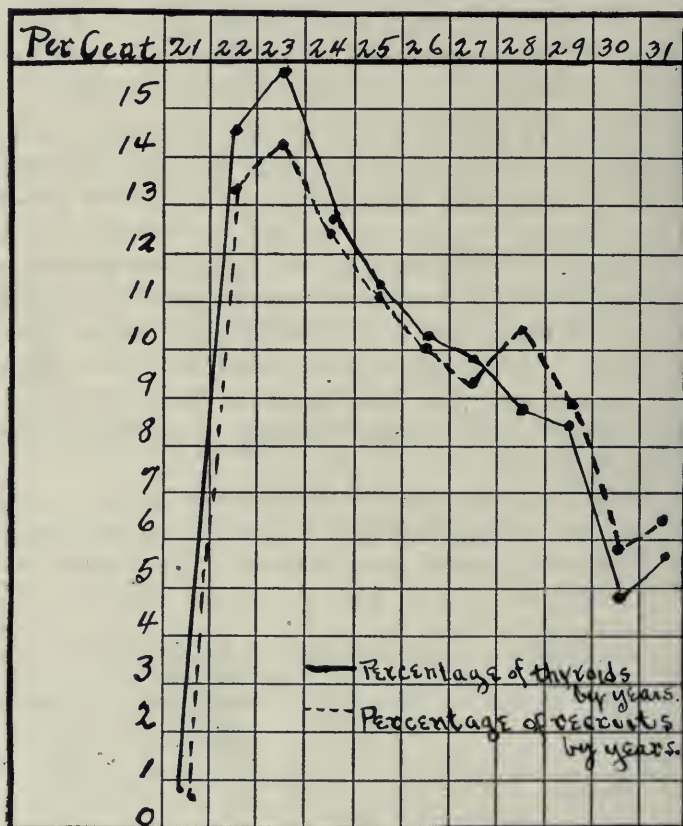


Chart 1

there was a relation between thyroid enlargement and the occurrence of several of the following objective abnormalities: (1) Tachycardia; (2) systolic murmur in the pulmonary area; (3) a second sound louder in the pulmonary than in the aortic area; (4) tremor; (5) moist blue hands, and (6) curved fingernails.

Limitations arising from the conditions under which the data had to be collected prevented the study of all these signs at this time. Only one member of the board could be spared from routine duties.

Since the primary object of the examination was to record all cases of enlarged thyroid and to determine the frequency of the condition in the total draft, it was necessary to examine every man. Thus, more than one thousand recruits commonly passed through the examiner's hands every day, and it was not found possible to make records of pulse rate or to examine with sufficient accuracy for the absence or presence of the auscultatory cardiac signs which it was supposed might have some association with the thyroid enlargement. Experience soon showed that one man could not do more than record the absence or presence of goiter and note in those cases in which it was present whether the enlargement came under the terms small, moderate or large as defined in the previous section, and whether the enlargement was diffuse or apparently localized to the isthmus or the right or left lobes. After this there was time only to note the absence or presence in goiter cases of tremor, moist blue hands and curved nails.

In addition to the limitations imposed by the shortness of the time available for the examination, there was another arising from the fact that the great majority of the men had received their first injection of typhoid vaccine at some time within the twenty-four hours preceding the examination. The constitutional disturbance arising in many of the men from this cause was, as we found later, a considerable factor in determining the frequency of the above signs. It was early recognized also that pulse rates obtained under these circumstances could have only a very limited significance.

The meaning of the figures obtained by this examination can of course only be determined by comparison with those obtained from a group of individuals observed under the same conditions who had no thyroid enlargement. Similar data were therefore also collected from as many nongoiter individuals as time allowed.

In view of the necessarily unfavorable conditions attending the examination the board does not regard the figures relating to the incidence of tremor, etc., as in the nature of more than a rough preliminary survey. The main object was to determine the frequency of endemic goiter in men coming to Camp Lewis. The further study of various signs present in cases with thyroid enlargement is now being undertaken in men of the June and July drafts and will be reported later.

#### DEFINITION OF SIGNS

There is a large personal factor in dealing with such signs as tremor, moist blue hands and curved nails, even though no attempt is made to attach any quantitative value to them. It is therefore of great importance that all the work be done by one man. This unfortunately was not possible, since Lieutenant Moran, who commenced the work,

was ordered elsewhere before it was completed. In spite of an attempt to conform to the same standards, the figures of his successor varied appreciably from those obtained by him. No absolute value can therefore be attached to the figures given. Greater significance, however, is found in the comparison of the incidence of these signs in nongoiter as opposed to goiter cases, and here there was a uniformity of standards for the same observer saw all the members of both groups.

#### TREMOR

The arm was extended at right angles to the body with the fingers extended. The very slight tremor which is not uncommon in apparently normal individuals and which is somewhat difficult to make sure of, was disregarded. Very coarse, incoordinate movements of individual fingers were also ruled out. It was found that a distinct tremor was sometimes present in only one finger, commonly the index finger, and was absent in others. These cases were not counted.

Of the total number of men with enlarged thyroids 2,591, or 55.0 per cent., had tremor.

#### MOIST, BLUE HANDS

The incidence of this sign naturally varies considerably with changes in the temperature and humidity of the air. Those cases were counted in which there was a clearly apparent degree of cyanosis of the hands, and in which palpation of the palms revealed a definite moisture.

Of the total number of men with enlarged thyroids 4,123, or 88.0 per cent., had moist, blue hands.

#### CURVED NAILS

By curved nails is meant an anteroposterior curving which was present to a marked degree not only in the first and second but also in the third and fourth finger nails.

Of the total number of men with enlarged thyroids 2,612, or 56.0 per cent., had curved finger nails.

#### COMPARISON OF THE INCIDENCE OF TREMOR, MOIST, BLUE HANDS AND CURVED NAILS IN GROUPS OF MEN WITH AND WITHOUT THYROID ENLARGEMENT

This comparison entailed such a considerable increase in the amount of work that the examination had to be very hurriedly conducted in order to prevent delay in the passage of men from one examining board to the other. For this reason it was not possible to carry this through as a routine. The percentage figures for the two groups are given in Table 6.

The results of this comparison were not those expected by the Board. The impression had been gained that the above signs were much less frequent in nongoiter cases than is actually shown by these figures. This fact seems to make it all the more important that more accurate data under more satisfactory conditions of examination be obtained as to the relative incidence of these signs. A report of this more detailed examination will be forwarded shortly.<sup>1</sup>

TABLE 6.—COMPARISON OF A GROUP OF 1,138 RECRUITS WITHOUT THYROID ENLARGEMENT AND OF A GROUP OF 1,397 RECRUITS WITH THYROID ENLARGEMENT AS REGARDS THE PERCENTAGE FREQUENCY OF CERTAIN SIGNS

Sign	Nonthyroids	Thyroid
Tremor .....	44.0	54.0
Moist, blue hands.....	76.0	95.0
Curved nails.....	64.0	75.0

#### GEOGRAPHICAL DISTRIBUTION

*F. State Distribution.*—The geographic distribution outlined in the tables and maps of this section refers only to the distribution of enlarged thyroids, as we have defined that term, in men between the ages of 21 and 31. But it may be noted that the distribution throughout the whole population will relatively correspond closely with that which we have deduced from this special section of the community.

The distribution among the various states of all cases classed as having enlarged thyroids is given in Table 7.

TABLE 7.—THE NUMBER AND PERCENTAGE OF ENLARGED THYROIDS IN RECRUITS FROM DIFFERENT STATES ARRANGED IN ORDER OF DESCENDING MAGNITUDE

State	Percentage Enlarged Thyroids	No. of Enlarged Thyroids	No. of Recruits
Washington .....	39	826	2,114
Oregon .....	32	291	923
Montana .....	26	900	3,465
Idaho .....	26	362	1,395
Wyoming .....	25	128	516
Minnesota .....	22	1,023	4,714
Utah .....	22	318	1,434
North Dakota.....	17	212	1,230
South Dakota.....	14	252	1,848
Nevada .....	9	17	179
California .....	8	360	4,364

Washington and Oregon show the highest percentage, and Nevada and California the lowest.

On account of the fact mentioned in the previous section that under our particular definition many cases were included in which the seeming enlargement of the thyroid may not have been pathological, special

1. Addis, Thomas, and Kerr, William J.: Arch. Int. Med. **23**:316 (March) 1919.

attention is directed to Table 8, which gives the percentage in the different states of cases in which the thyroid was certainly enlarged far beyond any physiological limit.

TABLE 8.—THE NUMBER AND PERCENTAGE OF LARGE OR MODERATELY ENLARGED THYROIDS IN RECRUITS FROM DIFFERENT STATES ARRANGED IN ORDER OF DESCENDING MAGNITUDE

State	Percentage of Large or Moderately Enlarged Thyroids	No. Large or Moderately Enlarged Thyroids	Total No. Recruits
Washington .....	11.0	232	2,114
Oregon .....	8.6	79	923
Idaho .....	7.3	102	1,395
North Dakota .....	6.6	81	1,230
Montana .....	6.4	222	3,465
Utah .....	5.5	79	1,434
Minnesota .....	5.1	242	4,714
Wyoming .....	3.7	19	516
South Dakota .....	2.0	37	1,848
Nevada .....	1.1	3	179
California .....	0.5	23	4,364

It will be noted that the arrangement of the states is still the same at the extremes, but that the relative difference between such states as Washington and California is more pronounced when only grossly enlarged thyroids are dealt with. In Tables 9 and 10 are given the state distribution as regards the part of the thyroid gland in which enlargement was noted, and the incidence of goiter in the families of recruits with thyroid enlargement.

TABLE 9.—THE PORTION OF THE THYROID GLAND IN WHICH ENLARGEMENT WAS NOTED IN RECRUITS FROM DIFFERENT STATES

State	Percentage			
	Diffuse	Isthmus	Right Lobe	Left Lobe
Washington .....	61	32	4	3
Oregon .....	55	39	3	3
Montana .....	41	53	4	2
Idaho .....	57	35	5	3
Minnesota .....	21	58	11	9
Wyoming .....	48	50	1	1
Utah .....	28	35	5	3
North Dakota .....	30	67	2	1
South Dakota .....	25	72	2	1
Nevada .....	45	55	0	0
California .....	40	54	4	3

TABLE 10.—DISTRIBUTION OF GOITER IN THE FAMILIES OF RECRUITS WITH THYROID ENLARGEMENT FROM DIFFERENT STATES

State	Sister	Mother	Brother	Father
Washington .....	50	27	20	3
Oregon .....	58	20	21	1
Montana .....	47	35	17	2
Idaho .....	48	33	17	2
Minnesota .....	55	28	13	3
Wyoming .....	52	28	14	7
Utah .....	53	26	15	5
North Dakota .....	57	31	8	4
South Dakota .....	55	37	8	0
Nevada .....	80	20	0	0
California .....	39	37	21	4

The relative distribution of enlarged thyroid glands among the different states is represented by means of different depths of shading in Chart 2.

#### CONCLUSIONS

1. A survey of 21,182 troops coming to Camp Lewis, Washington, from eleven states, comprising an area of approximately one third of the United States, shows a high incidence of simple goiter in certain regions. The incidence is highest in Washington and Oregon, and lowest in California and Nevada. There is an area of endemic goiter largely confined to the Pacific Northwest, and shading off to the south



Chart 2.—Relative distribution of enlarged thyroid glands among different states.

and east. There is again a slight increase in Minnesota which should be considered as a part of the endemic goiter region adjacent to the Great Lakes.

2. Exophthalmic goiter was very rarely seen in troops coming to this camp, although many recruits were rejected because of thyroid enlargement producing pressure symptoms or interfering with the wearing of the military collar. Cases of exophthalmic goiter were rejected by the local boards.

3. Twenty-one per cent. of all troops examined showed a definite enlargement of the thyroid gland. Of these, 27 per cent. showed a

large or moderately enlarged thyroid, and 73 per cent. were classified as "small." In the latter group only those in whom the gland could be distinctly felt on swallowing were included.

4. The enlargement of the thyroid gland was noted as diffuse in 38 per cent. of the cases, isthmus in 52 per cent., right lobe in 5 per cent., and left lobe in 4 per cent.

5. The family history of recruits with enlarged thyroid glands showed that goiters had been noted in sisters three times more frequently than in brothers, and in mothers ten times more frequently than in fathers.

6. There was no evidence to show that the thyroid gland diminishes in frequency between the ages of 21 and 31 years.

7. Such physical signs as tremor, tachycardia, vasomotor instability of the hands and curved nails, were noted, and were found in a larger percentage of men with thyroid enlargement than in those without demonstrable changes in the thyroid. The differences, however, were not striking, and no definite conclusions can be drawn at this time.

8. No definite conclusions can be drawn as to the etiologic factors in the production of endemic goiter. The region affected roughly corresponds to the glaciated areas of the United States. There is apparently some relation to the water supply.

9. The geographic distribution has been shown by states. Similar statistics by counties in each state have been compiled, but for want of space are not included in this report.

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## THE PRODUCTION OF BRIGHT'S DISEASE BY FEEDING HIGH PROTEIN DIETS \*

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For nearly a century the etiology of Bright's disease has been the subject of much medical thought and investigation. But in spite of this, the clinician is still unable to find a cause for the disease in the great majority of cases seen by him. The present investigation was undertaken with the hope of throwing some additional light on this difficult subject.

The chief business of the kidneys is to rid the organism of the end products of protein metabolism. This task is accomplished to a considerable extent by active secretion on the part of certain portions of the tubular epithelium. These cells will not only remove normal waste, but they will also remove from the blood stream substances which are foreign to it even though they may be severely injured by the poisons passing through them. Thus investigators<sup>1</sup> have shown that when the kidney eliminates such substances as mercury, or the salts of uranium and chromium, a high grade tubular nephritis may be produced; and that the acute tubular injury may be followed by a chronic nephritis.

The substances dealt with by this group of investigators do not play any considerable rôle in the causation of clinical nephritis. But the experiments demonstrate a fact of great importance, namely, that the tubular epithelium may suffer any degree of injury including death as a result of its efforts to remove certain abnormal substances from the blood.

The degree of injury produced by the nephrotoxic substances is largely dependent on their concentration in the blood. Thus mercury in therapeutic doses usually has no detectable effect on the kidney; although when its use is long continued, albumin and casts may appear in the urine. But when swallowed in large amounts in soluble form, acute fatal nephritis may result. Whether mercury will injure the

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\* From the Department of Internal Medicine, University of Michigan.

1. McNider, W. deB.: J. M. Research **34**:177 (May) 1916.

kidney, is determined not alone by certain qualities inherent in mercury, but also by the quantity of mercury which passes through the kidney in a unit of time.

May this same principle be applied to the nitrogenous bodies habitually secreted by the renal cells? May it not be true that the kidneys can secrete a certain amount of nitrogenous matter for an indefinite period without suffering harm, but that they will be injured if the quantity of some or all of the nitrogenous substances secreted be increased and kept at the higher level for some time?

The experiments which form the substance of this paper were undertaken with the intention of discovering whether nephritis will be produced when the kidneys have been eliminating an unusually large amount of nitrogenous material over a considerable period of time.

To attain this end, rabbits were fed diets abnormally high in protein. The experiments fall naturally into three groups determined by the type of protein used.

Group A includes all those animals whose nitrogen metabolism was increased by means of egg white.

Group B consists of rabbits that lived on a diet high in protein because of the addition of casein.

The animals in group C were fed soy beans.

#### GROUP A.—THE EGG WHITE EXPERIMENTS

All the animals in this group received egg white, but the diets were of three different sorts, each planned with a different object in view. The group may accordingly be subdivided into three subgroups, 1, 2 and 3.

*Subgroup 1.*—The preliminary experiments of the investigation fall under this heading. The object was to determine as quickly as possible whether the ingestion of large amounts of protein would produce demonstrable injury of the kidney in a relatively short time.

For this purpose six rabbits were each fed the whites of two hard boiled eggs daily for one week. During this time they received no other food. Thereafter rabbits Nos. 1 and 3 each ate the whites of four or five hard boiled eggs, and, in addition, were each allowed from 25 to 50 gm. of carrots daily. The feeding was continued in this way for thirty days in the case of rabbit No. 1; and for thirty-eight days in the case of rabbit No. 3. Rabbits Nos. 2, 4, 5 and 6, after the first week, ate the whites of from three to four eggs and received no other food. This second period for these four rabbits lasted, respectively, nine, ten, fourteen and twenty days.

The urine of none of these six rabbits contained either albumin or casts, the day preceding the experimental diet. A persistent albumin-

uria developed during the experimental period in the case of each rabbit. It was noted as early as the third day in the urines of rabbits Nos. 1 and 6; and on the fifth day in the urines of rabbits Nos. 2 and 3. Casts were seen in the urines of four of the rabbits, Nos. 1, 2, 3 and 6.

Rabbit No. 5 was found dead on the nineteenth day of the experiment. The remaining rabbits were killed as soon as they refused to eat the hard boiled egg white.

Microscopic examination of the kidneys was made. In every instance cloudy swelling and congestion was seen. Numerous casts were present in the kidneys of each of the rabbits with the exception of No. 6.

What value shall be placed on the data obtained from these rabbits? These data are albuminuria, casts in the urine and numerous casts seen in the microscopic sections of the kidneys, cloudy swelling and congestion. The last two, swelling and congestion, are features which all histologists recognize as variables. They are, in part, at least, related to the preparation of the tissues for microscopic examination. Taken by themselves, in the absence of other signs, they are feeble evidence of renal damage due to high protein diets.

What significance has the albuminuria? Is the albumin in the urine merely white of egg, absorbed as such from the intestine and filtered out of the blood as such by the kidney? It has been clearly demonstrated that this is not the cause of the albuminuria, but that the albumin found in the urine comes from the rabbit itself. The evidence appears in the following two experiments.

EXPERIMENT 1.—Rabbit No. 8, March 1, 1917. The diet has consisted entirely of hard boiled egg white for the past six days. The rabbit has a well marked albuminuria. Ten c.c. of blood are withdrawn from the heart. It is defibrinated by beating and the plasma is obtained by centrifuge. One c.c. of the whole plasma and 1 c.c. of each of the following dilutions, 1:10, 1:20, 1:50, 1:100, are placed in a series of tubes. To each tube 1 c.c. of a 1:1,000 solution of Kaulbaum's egg white is added. The tubes are kept at 38 C. over night. No precipitate is seen in any of the tubes the next morning.

A rabbit whose urine contains albumin consequent to the ingestion of egg white shows no detectable trace of the egg white in his blood.

EXPERIMENT 2.—Rabbit 13, Feb. 12, 1917. The diet has consisted entirely of hard boiled egg white for the preceding ten days. The urine shows a well marked albuminuria. One c.c. of this urine is injected into the peritoneal cavity of each of four guinea-pigs.

Blood is also withdrawn from the heart of this rabbit. It is allowed to clot and the serum is obtained by centrifuge. One c.c. of this serum is injected into the peritoneal cavity of each of four guinea-pigs.

February 24. The guinea-pigs which received the intraperitoneal injection of albuminous urine twelve days ago, are today each given intraperitoneally, 2 c.c. of a 1:100 solution of Kaulbaum's egg white. No reaction is observed.

One-half hour later, two of these same guinea-pigs are given an intravenous injection of normal rabbit's serum. Both showed typical anaphylactic shock.

The group of guinea-pigs which received the intraperitoneal injection of serum obtained from Rabbit 13, twelve days ago, today are each given intravenously 2 c.c. of a 1:100 solution of Kaulbaum's egg white. No reaction is observed. One-half hour later these same guinea-pigs are given an intraperitoneal injection of normal rabbit's serum. Typical anaphylactic shock resulted.

The intraperitoneal injection of the albuminous urine from a rabbit eating egg white, failed to sensitize guinea-pigs to egg white, but did sensitize them to rabbit's serum albumin. The intraperitoneal injection of serum obtained from a rabbit eating egg white failed to sensitize guinea-pigs to egg white, but did sensitize them to rabbit's serum albumin.

The albuminuria produced by feeding egg white may accordingly be accepted as satisfactory evidence of renal injury.

Casts are agglomerations of broken down renal epithelium. They are not found in the urines of normal rabbits. A very few casts may occasionally be found in the sections of supposedly normal rabbit kidneys. Their presence in large numbers in the urines and in the kidneys of the rabbits that received the egg white, is an unquestionable sign of kidney injury.

There is, then, clear evidence that a diet restricted to egg albumin with or without the addition of a small amount of carrot, is capable of quickly causing some renal damage.

*Subgroup 2.*—These experiments were planned with the object of showing whether recurring periods of excessive protein metabolism would injure the kidneys.

The animals were fed as much hard boiled egg white as they would eat for intervals of about nine days, alternating with periods of stock diet lasting about a week. This type of feeding was continued as long as the rabbits would eat the egg white.

There are four satisfactory experiments, lasting, respectively, four, four and one-half, five and one-half and six and one-half months. Three of the rabbits ate about three egg whites daily. One rabbit (No. 9) ate about five egg whites daily.

This rabbit was found dead at the end of six and one-half months. The microscopic examination of the kidneys revealed cloudy swelling, marked congestion, hemorrhage into the subcapsular space compressing the tufts and many casts. The kidneys of another one of these rabbits (No. 10) showed abnormalities of the same sort, but less well marked.

Both these animals were found dead. The necropsies revealed no important disturbances other than those found in the kidneys. Rabbit No. 9 had, however, lost 600 gm., and rabbit No. 10 lost 900 gm.

during the experimental period. Death may, accordingly, have been caused by inanition.

The two remaining animals of this group were killed. Their kidneys showed no changes which could certainly be attributed to the effect of the diet.

The urines of each of the four rabbits contained albumin during the experimental period.

The ingestion of large amounts of egg white as administered in this subgroup does not cause any serious chronic renal lesions, but evidence of some kidney disturbance has been obtained. No further conclusions are warranted.

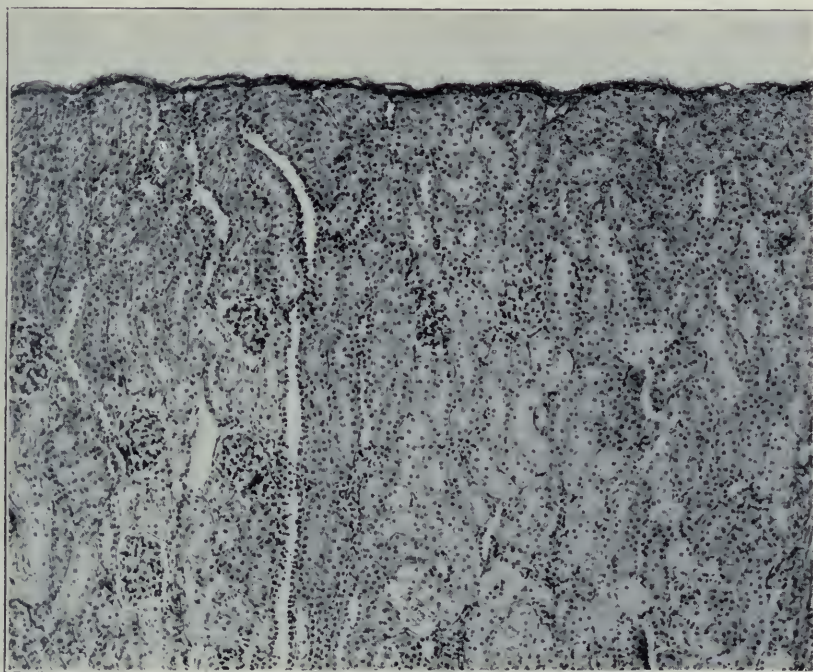


Fig. 1.—Microphotograph of the kidney of a normal rabbit.

*Subgroup 3.*—All the animals thus far dealt with lost weight while living on the experimental diets. It might be contended that the malnutrition was at least partly responsible for the renal injury. In order to obviate this possible source of error, a third series of rabbits was fed the egg white combined with other food in such a way as to guard against nutritional disturbances.

Each animal received the following mixture daily: three egg whites; 30 gm. of corn meal; sufficient bran (about 25 gm.) to make a stiff paste when the three ingredients were stirred together. The mass was

then transferred to a buttered pan and baked in a hot oven for about twenty minutes. In addition to this, each animal received 25 gm. of bread daily, and some cabbage or a carrot several times a week. This diet furnishes about 230 calories daily. It contains about 17 gm. of protein, about 33 gm. of carbohydrate, and about 2 gm. of fat. One third of the dry weight of the diet is protein.

Three rabbits, Nos. 110, 111 and 113, ate this diet for six months, four months and seven months, respectively. No. 110 maintained its weight, No. 111 gained about 450 gm., and No. 113 gained about 225 gm. The urine of each of the animals showed a marked albuminuria, and many granular and hyaline casts on every examination.

Rabbit No. 110 was killed at the end of six months. It had shown no sign of disease other than the abnormal urine. At necropsy the organs revealed no gross abnormality. Microscopic examination of the kidneys did not disclose any abnormalities which could be attributed to the diet.

Rabbit No. 111, after four months of the diet, began to refuse the egg white mixture and was accordingly killed. The kidneys weighed 21 gm., which is about twice the normal average. On microscopic examination, severe parenchymatous injury was seen. This was especially marked in the convoluted tubules whose epithelium showed granulation, swelling, vacuolization and desquamation. Some nuclei were unstained, others were much swollen. There were many casts in the convoluted and collecting tubules. The glomeruli were somewhat swollen, but there was no exudate in the subcapsular space. Many tufts showed extreme congestion. There was a little increase of young connective tissue in the cortex. Edema and engorgement were marked throughout the section.

Rabbit No. 113 ate the diet containing the whites of three eggs for seven months. During this time he gained 225 gm. and showed no signs of disease other than albuminuria and cylindruria. At the end of this period, the diet was changed so that it contained the whites of five eggs daily. None of the other factors in the ration were altered. The animal ate this latter diet for three months. During this period he gained about 330 gm. and appeared to feel exceptionally well. At the end of these three months he was killed. For seven months he had ingested three egg whites daily and for the next three months he had eaten five egg whites daily.

At necropsy the kidneys were found to weigh 22 gm., which is about twice the normal. The microscopic examination of the kidneys showed a well marked injury of the tubular epithelium, especially severe in the convoluted tubules. Desquamation, vacuolization and irregular disappearance of the parenchymatous cells was widespread.

Casts were numerous. In places, dilatation of tubules was seen. The kidney as a whole showed engorgement and edema. The glomeruli showed no specific injury. There was no fibroblastic increase. The thoracic aorta from the aortic valves to the diaphragm showed very many raised yellow plaques and streaks.

A fourth rabbit, No. 112, was fed the hard boiled egg white as such instead of the mixture of egg white, corn meal and bran. He also ate 50 gm. of bread and a few greens daily. This diet furnished about 180 calories daily. The rabbit took this diet well for three months. During this time he lost 200 gm. Thereafter, for the next

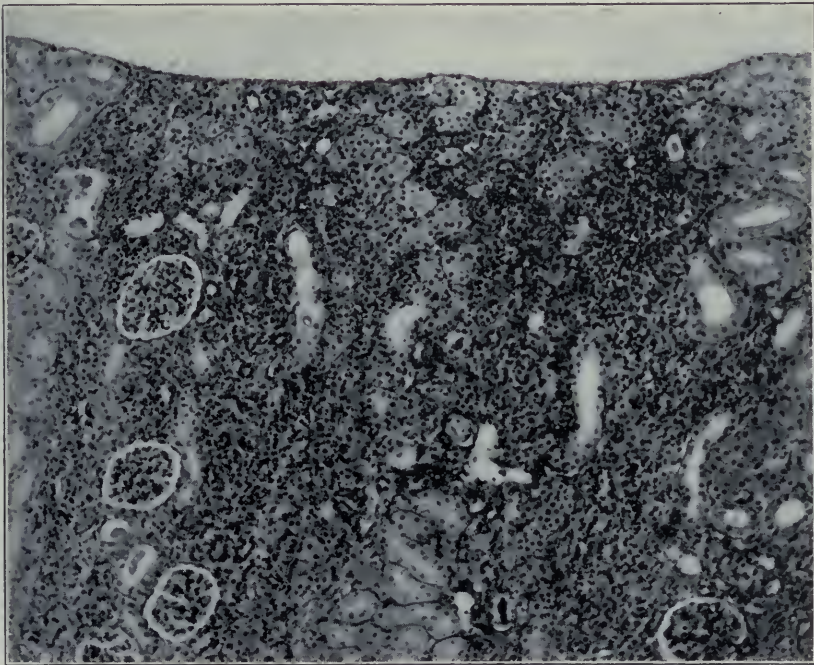


Fig. 2.—Early stage of chronic nephritis produced by the soy bean diet. Note the beginning contraction of the cortex and the pinching off of a group of tubules by connective tissue. Casts are seen.

ten days he ate only the egg white. Two or three days before he was killed he began to show marked weakness. This increased until he became ataxic and unable to hold up his head. He lost 330 gm. during these ten days. He was then killed by a blow on the head. At necropsy a few small areas of pulmonary congestion were found. The kidneys were pale and cloudy. They weighed 15 gm. (average normal is 11.8 gm.). The urine obtained from the bladder contained a large amount of albumin, many granular and hyaline casts, and numerous red blood cells. The microscopic examination of the kidney gave clear

evidence of severe acute injury. Many glomeruli were crowded with red blood cells. Masses of red blood cells and desquamated epithelium were seen in a few subcapsular spaces. The tubular epithelium, and more especially that of the convoluted tubules, showed granulation, much desquamation and marked vacuolization. Red blood cells were seen in the lumen of a few tubules. Some nuclei were swollen, while others were unstained. There were many casts in all parts of the tubules. The collecting tubules were dilated. This experiment presents an example of acute Bright's disease caused by the ingestion of large amounts of protein in the form of egg white.

At first sight it would appear as if the egg white diet had had a greater effect on this rabbit than on any of the three preceding ones which had eaten the same amount of egg white for longer periods. But a consideration of the nitrogen metabolism<sup>2</sup> of these three rabbits shows that such a conclusion would be incorrect. The total urinary nitrogen eliminated during five days was determined for each of these rabbits. The average twenty-four hours' amount for the rabbits that ate the egg white cooked with corn meal and bran was as follows: Rabbit No. 110, 1.2 gm. total nitrogen; rabbit No. 111, 1.5 gm. total nitrogen; rabbit No. 113, 1.2 gm. total nitrogen while eating the mixture containing three egg whites, 2.3 gm. total nitrogen while eating the mixture containing five egg whites; rabbit 112, 2.2 gm. total nitrogen. Obviously, the mixture of egg white with corn meal and bran resulted in a very poor absorption of the digestion products of the egg white. But when plain egg white was fed the absorption was excellent, and adequately explains the much more acute injury to the kidney observed in rabbit No. 112.

These data for the nitrogen metabolism of the four rabbits in this subgroup have a further significance. It will be noted that rabbit No. 110, whose twenty-four hours urinary nitrogen was only 1.2 gm., showed no renal changes which could be recognized by the microscope. The absorption of nitrogen from the diet was so poor in this instance as to result in only a slight increase over the normal nitrogen metabolism. The average total twenty-four hours urinary nitrogen in one group of controls was 0.8 gm.; in a second group it was 1.0 gm. Rabbit No. 111, whose absorption was better, 1.5 gm. total nitrogen, showed a subacute nephritis, but was able to gain weight and appeared to feel well up to the time when he was killed four months from the beginning of the experiment. Rabbit No. 113, whose absorption was only 1.2 gm. while he was eating a mixture containing the egg whites, gave no evidence of disease except albumin and casts during the seven

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2. A full discussion of the procedure used for determining the urinary nitrogen will be found in the discussion accompanying Table 2, page 375.

months of this diet. The change in his diet which caused him to eat five egg whites daily for the next three months, resulted in a nitrogen absorption of 2.3 gm. daily. He continued to gain weight and to give the outward appearance of health during this second period. But in spite of the steady gain in weight, the autopsy revealed a well marked subacute parenchymatous nephritis.

The data obtained from these four rabbits in Subgroup 3, demonstrate that the renal lesions observed were not a part of a nutritional

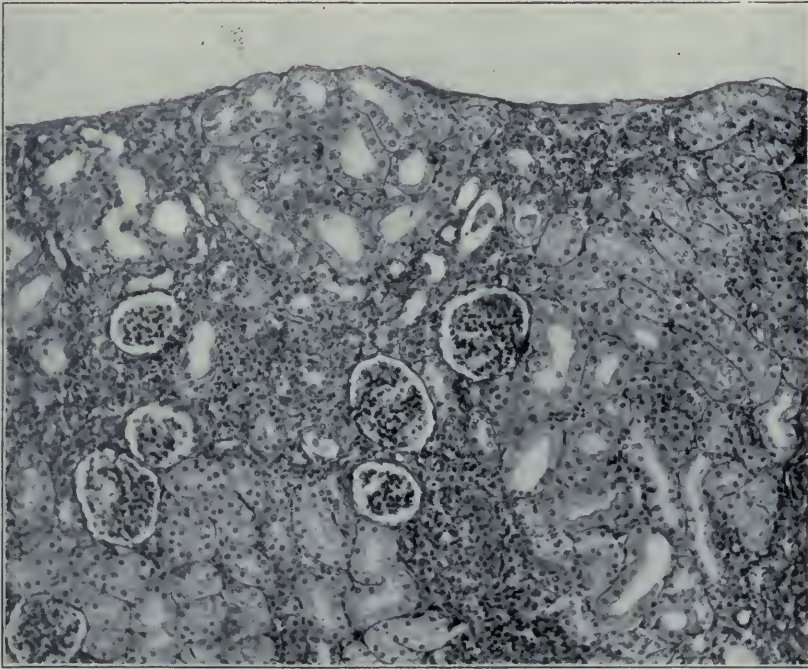


Fig. 3.—A later stage of the soy bean nephritis showing more marked contraction, atrophy of some glomeruli, slight thickening of Bowman's capsule and casts. A broad band of connective tissue occupies the central portion of the field.

disturbance, but were, in fact, the direct result of the injection of egg white.

The information obtained from the various types of experiments with egg white may be summed up by the following statements: (1) When rabbits eat several egg whites daily, evidence of renal injury is very quickly and constantly noted. (2) When rabbits absorb the digestion products of egg white in sufficient quantity for a considerable time, a well marked acute or subacute nephritis may result.

## GROUP B.—CASEIN EXPERIMENTS

In order to decide whether the nephritis observed in the preceding group of experiments was the result of the prolonged secretion by the kidney of an excessive amount of one or more of the nitrogenous bodies which, in lesser amounts, are normal constituents of the blood; or whether it might possibly have been caused by some nephrotoxic substance peculiar to egg white, it was necessary to determine whether nephritis would follow the prolonged ingestion of some other protein in excessive amounts.

Casein was chosen for this purpose. The diet was prepared by placing 25 c.c. of milk, 20 c.c. of water and 20 gm. of scraped carrot together in a pan over a hot water bath. When the mixture was warm, the casein and about 1 gm. of sodium bicarbonate was added. The whole was stirred. The gas evolved produced a porous mass which, when cool, somewhat resembled a "baking powder biscuit." Four rabbits were fed 30 gm. of casein daily in this way. Two rabbits received fifteen grams daily. In addition to this the animals received from 25 to 50 gm. of bread daily and a handful of greens about once a week.

The four rabbits which ate 30 gm. of casein daily, were killed at the end of three weeks, ten weeks, four months and eleven months.

The rabbit which was allowed to live only three weeks on the diet, was found acutely ill one morning, and for this reason the experiment was ended. The kidneys weighed 22 gm., or 7.5 gm. per kilogram. (The average weight of the kidneys of eight normal rabbits was 11.8 gm., or 4.9 gm. per kilogram.) On microscopic examination the kidney showed very marked edema and engorgement. There were numerous red blood cells scattered through the subcapsular spaces and the lumina of the tubules. Very many casts were seen. The other organs were normal. The type of renal disturbance found strongly suggests that the symptoms had been caused by acute nephritis.

The second rabbit had seemed to be ill for some days prior to his death. He was killed after he had been eating 30 gm. of casein daily for ten weeks. The kidneys weighed 20 gm.; and, on microscopic examination, showed moderate parenchymatous injury, casts and congestion.

The third rabbit, killed after four months of the diet, showed changes similar to those found in the preceding one, but they were much more pronounced. The kidneys weighed 21 gm.; and, on microscopic examination, revealed marked congestion, severe parenchymatous injury, very many casts and beginning fibroblastic increase.

The fourth rabbit that ate 30 gm. of casein daily was killed at the end of eleven months. The urine contained no albumin before the

casein diet was started, but did give positive tests for albumin thereafter. The kidneys weighed 16 gm., but gave no other evidence of injury due to the diet. Evidently, the high protein diet had either had less effect on the kidneys of this rabbit than upon those of the three preceding animals, or else this fourth rabbit had recovered from a nephritis such as was observed in the others at a much earlier stage of the diet. No choice between these two alternatives is possible.

Two other rabbits ate 15 gm. of casein daily for one year. Their urines showed no albumin before the diet was started. During the course of the experiment the slightest trace of albumin was often noted,

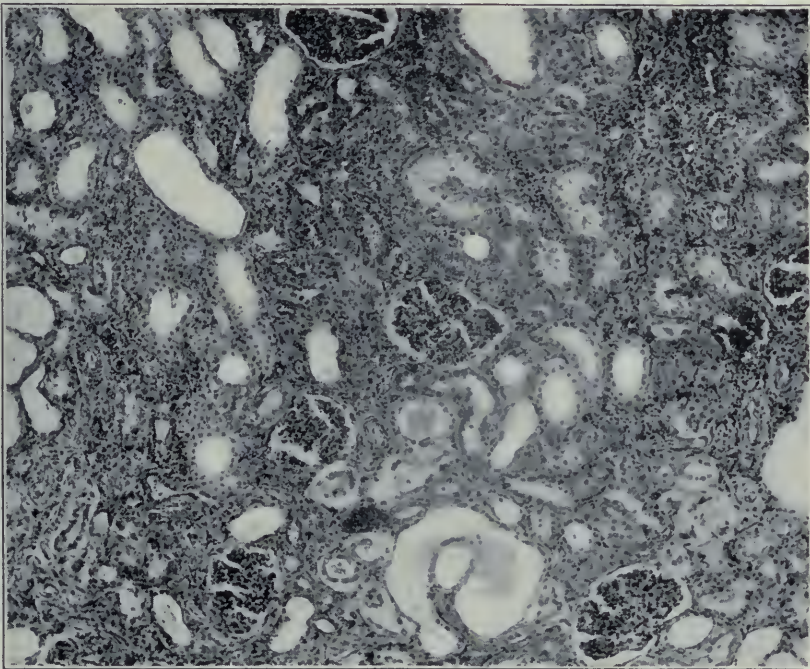


Fig. 4.—A still later stage of the soy bean nephritis showing marked injury of the epithelium of the convoluted tubules. Many convoluted tubules are lined by a flat epithelium; others have entirely lost the epithelial lining. Many tubules are widely dilated. There are many casts. Bowman's capsule shows more thickening. A patchy increase of connective tissue involving most of the field is seen.

but only once were a few casts seen. The kidneys weighed 13.5 gm. and 14.5 gm., respectively. Microscopic examination did not show any abnormalities.

The outcome of the experiments with casein is this: When the nitrogenous metabolism is increased by means of casein, rabbits suffer no renal injury from eating 15 gm. of casein daily, even though this

amount of casein causes the nitrogen metabolism to be about double the normal. But when the daily intake of casein is 30 gm., and the nitrogen metabolism is about three times the normal, a well marked deleterious effect on the kidney was produced in three rabbits out of four.<sup>3</sup>

#### GROUP C.—SOY BEAN EXPERIMENT

Even though there can be little doubt that the kidney lesions thus far described bear a causal relation to the large amount of protein in the diet, nevertheless it was felt that the evidence would be strengthened if similar results should be obtained by feeding a third type of protein.

For this purpose soy beans were used as the sole food. The soy bean was chosen for a number of reasons: (1) Rabbits habitually eat vegetable protein. A renal injury occurring in herbivora as a result of the ingestion of a large amount of vegetable protein would have more significance than if it had been produced by means of an animal protein. (2) It was to be expected as the result of the studies of Osborne and Mendel,<sup>4</sup> and of Daniels and Nichols,<sup>5</sup> that animals could live on the soy bean<sup>6</sup> for many months without acquiring nutri-

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3. The necropsies of the three rabbits whose casein feeding had lasted for a year, revealed an unexpected lesion of great interest. The thoracic aorta in each case was the seat of a well marked arteriosclerotic process. The inner surface of the aorta presented many raised yellow plaques and streaks. The lesion was most extensive at the very beginning of the aorta and included the aortic valves. It gradually became less marked as one passed down the aorta and ended before the diaphragm was reached. None of the other large vessels were involved. The microscopic appearance of the lesion was described by Dr. C. V. Weller as follows: "Rabbit 58. Aorta. Hemalum and eosin and Van Gieson's stains. The intima is thickened irregularly through the presence of elevated plaques, many of which are three to four times as thick as the normal aortic wall. These elevated patches in most cases involve only the intima. In a few instances the innermost lamellae of the media are included. The elevated patches show a proliferation of the intima, increase in the elastic fibers and large areas of secondary fatty degeneration and liquefaction necrosis, accompanied by marked formation of cholesterol. The picture is that of an advanced intimal atherosclerosis in varying stages up to and including secondary atheromatous change with cholesterol formation. The greater part of the media and the adventitia are negative."

This disease of the aorta was found only in the three rabbits that had eaten the casein diet for a year and in the one rabbit (No. 113) of the egg white group that had eaten the egg albumin for ten months. Further study is required to determine whether arteriosclerosis may be regularly caused by the prolonged injection of high protein diet.

4. Osborne, T. B., and Mendel, L.: *J. Biol. Chem.* **32**:369 (Dec.) 1917.

5. Daniels, A. L., and Nichols, N. B.: *J. Biol. Chem.* **32**:91 (Oct.) 1917.

6. Bulletin No. 28, Office Experiment Stations, Washington, D. C., states the composition of the soy bean as follows: water, 5.5 per cent.; protein from 36 to 43 per cent.; fat, 17 per cent.; ash, ?; carbohydrate (by difference), 34.5 per cent.

tional disturbances. (3) The soy bean is very rich in protein. The beans used by us contained 37.8 per cent. of protein. If the rabbits ate enough of the beans to maintain their weight, they would of necessity also eat very much more protein than was their habit.

Twenty-six rabbits were placed in a large pen consisting of three compartments. The dividing walls were made of wire netting. Some of the rabbits were full grown. The remainder were about six months old and about three fourths grown. The adults were all put in the first compartment. Six of the partly grown rabbits were kept in the second compartment. The remainder of the young rabbits were placed

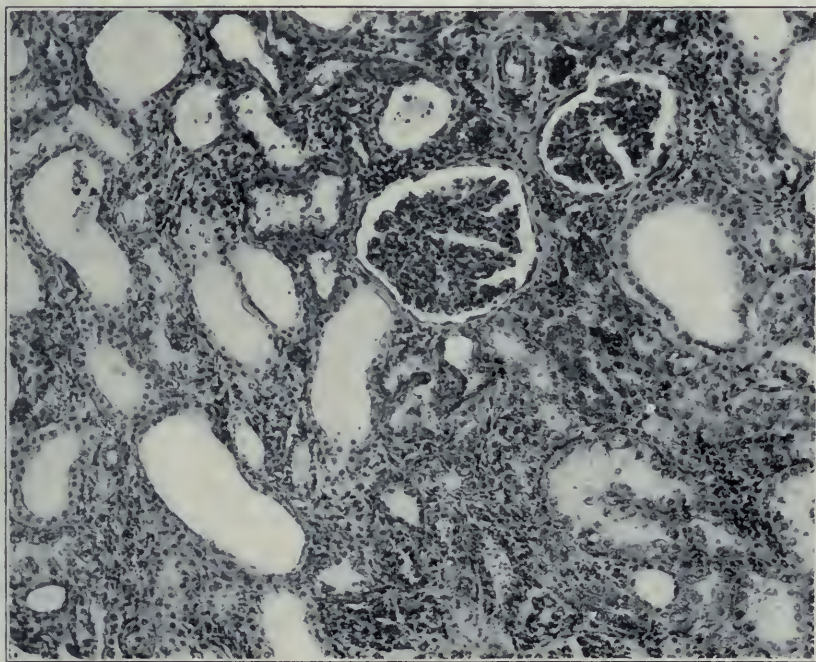


Fig. 5.—A higher magnification of the same field as Figure 4. Note especially the extreme atrophy and dilatation of the tubules.

in the third division of the pen. The six rabbits in the second compartment served as controls. They were fed hay, bread, corn cake, cabbage and other greens. The other two groups in the pen, consisting of twenty rabbits, lived on soy beans and water. All of the rabbits were exposed to the same conditions, except as regards diet. If at the end of the experiment any consistent difference between the kidneys of the control rabbits and of the soy bean groups should be found, this difference would have to be attributed to differences in diet.

The average individual weight of the control rabbits after seven months residence in the pen was 2,415 gm. The partly grown rabbits

averaged 2,179 gm. at the beginning of the soy bean diet. Three months later their average weight was 2,497 gm., an average individual gain of 318 gm. The average weight of the adults at the beginning of the soy bean diet was 2,382 gm. Three months later they weighed, on the average, 2,780 gm. At the end of another three months these animals averaged 2,892 gm. It is evident from a consideration of the above weights that the soy bean, when fed as the only source of food, is not alone adequate for maintenance, but also for growth.

The control rabbits were killed at the end of seven months. Neither the gross nor the microscopic examination of their kidneys revealed any abnormalities.

Of the twenty rabbits that were fed soy beans, five were killed at the end of two months. The kidneys of four of these animals showed no changes. But the kidneys of the fifth rabbit showed degeneration of the epithelium of the convoluted tubules and very many casts.

Fifteen rabbits lived on an exclusive diet of soy beans for from four and one-half months to twelve months. Eight of these fifteen rabbits died. Microscopic examination of the kidneys showed acute or chronic nephritis in every instance. In addition to this, two of the animals had pneumonia and one a bacterial endocarditis. In five of the eight animals that died while on the soy bean diet, no cause of death other than Bright's disease could be found. Seven of the fifteen rabbits were killed by a blow on the head after they had lived on the soy bean diet for from four and one half to twelve months. The microscopic examination of these kidneys showed, with one exception, subacute and chronic nephritis. The kidneys of one rabbit, killed at the end of five months, showed only slight injury of the tubular epithelium.

The following protocols and the microphotographs will illustrate the type of kidney lesion which develops in the rabbit as the result of a diet restricted to soy beans.

RABBIT 90.—Nov. 19, 1917: This is one of the young rabbits. He was about three-fourths grown at the beginning of the experiment. April 1, 1918: He was found dead this morning. He had eaten nothing but soy beans for four and one-half months. He weighs 1,590 gm. Necropsy: All organs except the kidneys appear to be normal. The bladder urine contains albumin and many hyaline casts. The heart weighs 7 gm. The kidneys weigh 12 gm. The capsule strips easily, leaving a smooth surface which presents a peppered appearance. Microscopic examination<sup>7</sup> of the kidney: "Patchy degenerative nephritis, shown by cloudy swelling, atrophy, dilatation of tubules and obliteration of some convoluted tubules by connective tissue. Bowman's capsule is thickened in many instances. There is some thickening of the arterial walls. The glomeruli show varying stages of atrophy, congestion of capillaries and degeneration of epithelium. Van Gieson's stain shows marked increase in

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7. I am grateful to Dr. A. S. Warthin for this and other descriptions of the microscopic anatomy of the kidneys.

connective tissue, especially marked in the labyrinths but extending into the medullary rays. There is very little cellular infiltration in these areas. Many granular and hyaline casts are seen."

RABBIT 98.—Nov. 5, 1917: Soy bien diet started.

June 25, 1918: After seven and one-half months of the diet the rabbit weighs 3,120 gm. Nov. 5, 1918: The rabbit has eaten nothing but soy beans for one year. It weighs 2,725 gm. Blood was withdrawn from the heart today. It contained 123 mg. of incoagulable nitrogen per 100 c.c., and 128 mg. of urea per 100 c.c. The urine shows a trace of albumin and a few coarsely granular casts.

The animal is now placed on a diet of greens, oats and bread. Nov. 17, 1918: It weighs 2,610 gm. November 18: The total incoagulable nitrogen of the blood is 89 mg. per 100 c.c.; the urea is 52 mg. per 100 c.c. December 2, 1918: The animal weighs 2,440 gm. The total incoagulable nitrogen of the blood is 123 mg. per 100 c.c.; the blood urea is 60 mg. per 100 c.c. The urine shows a trace of albumin but no casts.

A consideration of the figures for incoagulable nitrogen and blood urea shows that both were about twice the normal for rabbits, four weeks after this animal had been placed on a normal diet. The nitrogen retention is evidence of a serious disturbance in renal function. It is also worthy of special note that the animal lost 285 gm. during the last four weeks of his life in spite of the fact that he was receiving a normal diet. The continuous loss of weight under these conditions, indicates that the rabbit was seriously ill.

Dec. 3, 1918: Necropsy: All organs but the kidneys appear to be normal. They weigh 15 gm. The capsule strips easily, leaving a finely granular surface. Microscopic examination shows a well marked irregular increase in connective tissue. Just beneath the capsule, fairly large patches of connective tissue have caused contraction in these areas. The connective tissue extends in irregular bands through the cortex deep into the medulla. Many of Bowman's capsules are much thickened. Many glomeruli show atrophy, and a few, marked scarring. The convoluted tubules are dilated and lined with a flattened epithelium whose nuclei are picnotic. Desquamation of the tubular epithelium is seen in some places. There are many casts throughout the section.

The protocols and the photographs of the kidneys make it clear that the nephritis produced by the soy bean closely resembles the chronic nephritis commonly found in human subjects—the secondarily contracted kidney of the pathologists. The lesion is not the result of arteriosclerosis, for the arteries are not diseased. Nor are we dealing with a primary glomerulonephritis. Judging by the constancy and severity of the damage to the epithelium of the convoluted tubules, the firm impression is gained that the offending substance has its primary and chief deleterious effect upon the epithelium of these tubules and that this slowly progressing injury of the convoluted tubular epithelium is accompanied by an overgrowth of the connective tissue.

The soy bean nephritis causes a marked interference with renal function. There is an early and persistent retention of blood urea. Table 1 shows the blood urea readings in normal animals and in animals that had lived on soy beans for (1) seven weeks and for (2) six months. The normal animals ate hay, oats and bread. All the animals were fasted for twenty-four hours before drawing the blood.

This precaution was taken in order to avoid an error in favor of the nephritis rabbits. Since these animals were eating abnormally large amounts of protein, their blood urea might be abnormally high during the digestive period. But the undamaged kidney would eliminate any excess of blood urea from that source during the twenty-four hours' fast.

TABLE 1.—BLOOD UREA IN NORMAL AND IN SOY BEAN RABBITS

Normals		Rabbits Living on Soy Beans			
Hay, Oats, Bread		Seven Weeks		Six Months	
Number	Urea per 100 C.c.	Number	Urea per 100 C.c.	Number	Urea per 100 C.c.
A	42 mg.	33	83 mg.	—	—
B	33 mg.	34	90 mg.	—	—
C	17 mg.	35	84 mg.	35	176 mg.
D	36 mg.	36	96 mg.	33	118 mg.
E	29 mg.	37	98 mg.	37	78 mg.
F	33 mg.	38	98 mg.	38	87 mg.
Average	31 mg.	Average	100 mg.	Average	115 mg.

The experiments described above leave no doubt that a well marked chronic nephritis is produced in rabbits when the diet is restricted to soy beans. Evidence has been presented to show that the renal lesion is not the outcome of a lack of any essential food constituent. Nor can the lesion be attributed to an hypothetical nephrotoxic substance in the bean. For the habitual use of the soy bean by the Japanese and Chinese as food, and the excellent results obtained by Osborne and Mendel,<sup>4</sup> and by Daniels and Nichols<sup>5</sup> when the bean was the sole source of protein in the diet, make it highly improbable that the bean contains any poisonous substance which could so regularly and seriously damage the kidney of the rabbit. The only tenable explanation, in the light of the results obtained with egg white and casein, is one which relates the nephritis observed in each group of experiments, to the common factor, namely, the high protein content of the diet.

#### NITROGEN METABOLISM

Having now shown that nephritis may be produced in rabbits by feeding high protein diets, it is of interest to compare the nitrogen metabolism of such rabbits with that of rabbits eating a normal diet. To that end the following plan was used.

The rabbits used as normals were taken from a stock cage and placed in metabolism cages. They were fed oats and carrots, and allowed to eat as much of the weighed amount offered as they chose. The first twenty-four-hour specimen of urine was discarded. All the urine voided during the next five days was saved and measured.

Enough strong HCl was placed in the receptacles to make the urine acid. The urine was acidified to prevent loss of urea. It had been found previously that the urea in the alkaline rabbit urine gradually breaks down. The total amount of each food eaten during the five day period was determined, and the approximate amount of protein eaten was calculated from Atwater and Bryant's tables. The urines were analyzed for total nitrogen, urea nitrogen and ammonia nitrogen. All calculations were reduced to a twenty-four hour period. The normal data were obtained from six rabbits. Exactly the same procedure was followed with the three rabbits of Subgroup 3, eating egg white, three rabbits on casein diets and four of the rabbits living on soy beans.

TABLE 2.—PROTEIN EATEN, PROTEIN ABSORBED AND NITROGEN EXCRETED IN URINE

	Rabbit No.	Protein Eaten, Gm.	Protein* Absorbed, Gm.	Urine			
				Total N, Gm.	Urea N, Gm.	Urea, Gm.	Amount, C.c.
Controls	—	8.5	5.3	0.85	0.64	1.37	105
	—	11.2	5.7	0.91	0.50	1.07	109
	—	11.4	4.2	0.67	0.53	1.13	74
	—	8.0	4.5	0.72	0.59	1.26	107
	—	13.0	4.8	0.78	0.61	1.31	62
	—	9.7	5.7	0.91	0.89	1.90	90
	Average	10.3	5.0	0.81	0.63	1.34	91
Egg white	110	15.0	7.9	1.21	1.12	2.40	87
	111	15.0	9.2	1.48	1.44	3.08	120
	112	15.0	13.9	2.23	2.05	4.40	182
	113	15.0	7.4	1.19	1.17	2.50	155
	113	25.0	14.3	2.24	1.80	3.90	120
	Average	—	—	—	—	—	—
Casein	57	15.0	11.5	1.54	1.66	3.65	70
	58	15.0	11.9	1.91	1.87	4.0	93
	61	30.0	14.8	2.38	2.25	4.80	220
	Average	—	—	—	—	—	—
Soy Beans	38	16.7	8.2	1.32	1.08	2.31	114
	92	26.6	14.0	2.24	2.05	4.39	202
	96	19.0	12.9	2.07	1.83	3.92	111
	95	8.4	8.2	1.32	1.15	2.46	60
	Average	17.7	10.8	1.74	1.53	3.27	122

\* This figure is obtained by multiplying the total urinary nitrogen by 6.25.

Table 2 shows that when rabbits are living on what may be considered a normal diet, they eat by choice about 10 gm. of protein daily; but that they absorb only about 5 gm., or half of the protein eaten. The same relation holds in regard to the mixture of egg white, corn meal and bran. Rabbits which ate this mixture containing about 15 gm. of protein absorbed about 8 gm. of protein. When, however, plain, hard boiled egg white was fed, nearly all of it was absorbed. A correspondingly greater effect on the kidney was noted. The absorption of the digestion products of casein was

very good in the case of the rabbits that received 15 gm. of casein daily. They had a nitrogen metabolism of more than twice the normal. It will be seen from the table that the ingestion of soy beans by the four rabbits tested was quite variable. In order to get a more reliable figure for the average daily consumption of the beans, the amount eaten by eight different rabbits during seven-day periods was determined. The consumption was measured for thirty such periods. The resulting average was 40 gm. of beans eaten daily by each rabbit, with a variation from 22 to 80 gm. The beans used by us contain 37.8 per cent. of protein, hence the animals were eating 15 gm. of protein daily. This is somewhat less than the ingestion by the four rabbits during the test period. However, the individual averages of these four rabbits determined in the case of the first one from seven periods, for the second, third and fourth ones from four periods each, gave the following average intakes: 13.9 gm., 18.1 gm., 17.0 gm., 12.0 gm. The average is 15 gm., which is the general average. The figure found in the table for average protein absorption is probably also a little high, but cannot be far from correct. Accordingly, it may be stated that the protein metabolism of rabbits whose sole food is the soy bean, is about twice the normal.

When these figures for protein absorption from the various diets are compared with each other, it is seen that a chronic nephritis is produced when soy beans are eaten in sufficient quantity to double the total nitrogen metabolism. But casein and egg white must be fed in sufficient amounts to treble the total nitrogen in order to injure the kidney seriously; and furthermore, the injury from both casein and egg white tends to be acute rather than chronic. Apparently, the kidney is not injured by the secretion of that portion of the total nitrogen which is formed in amounts corresponding to the quantity of protein absorbed, for if that were the case, the injury to the kidney would be expected to be proportionate to the amount of protein absorbed, regardless of the source; and urea, which is the quantitatively important end-product of all protein metabolism, would be expected to damage the kidney in proportion to the amount secreted by it. But a comparison of the urea figures for soy bean rabbits with the average urea output of three rabbits eating casein, shows that the soy bean produced nephritis in rabbits that were secreting 3.3 gm. of urea daily, whereas the casein food failed to produce nephritis in rabbits whose urea averaged 4.1 gm. daily. This question was investigated further by feeding 5 gm. of urea daily to three rabbits that were eating an otherwise normal diet. The rabbits ate the urea for two, three and nine months, respectively. Analysis of the urine for urea showed that they were eliminating a little more than twice the normal amount. The

urines occasionally contained the slightest trace of albumin, but never any casts; and microscopic examination of the kidneys failed to show any abnormalities which could be attributed to the urea. It may accordingly be definitely stated that the renal lesion produced by feeding high protein diets is not caused by the passage of too much urea through the kidney.

It would appear rather that the kidney injury was related to those digestion products of protein which vary both quantitatively and qualitatively with the type of protein eaten. In this connection, one thinks of the amino acids. They form a constant constituent of the urine, and the quantity of amino acid nitrogen found in the urine is proportionate to the protein metabolism. On the other hand, individual members of the group are found in large amounts in some proteins and are nearly absent from others. Whether the amino acids are responsible for the nephritis can only be determined by studying their effect on the kidney. At present, no data which will throw any light on this question are available.

#### SUMMARY

In the majority of cases of chronic Bright's disease the cause of the nephritis cannot be discovered. This investigation has been undertaken with the intention of determining whether the elimination of abnormally large amounts of nitrogenous material by the kidney will cause nephritis. To this end, high protein diets have been fed to rabbits. The following results were obtained:

1. Renal injury was very quickly and constantly noted in rabbits that ate several egg whites daily.

2. Prolonged egg white feeding caused acute and subacute nephritis.

3. When the nitrogenous metabolism was increased by means of casein, rabbits suffered no demonstrable renal injury from eating 15 gm. of casein daily; but when the daily intake of casein was 30 gm., and the nitrogen metabolism was about three times normal, a well marked deleterious effect upon the kidney was produced.

4. Rabbits that lived on soy beans for months regularly acquired chronic nephritis and frequently died of it. The nitrogen metabolism from this diet was about twice the normal.

5. The renal lesion produced by feeding high protein diets was not caused by the passage of too much urea through the kidney.

The data suggest that the kidney injury is related to those digestion products of protein which vary both quantitatively and qualitatively with the type of protein eaten.

## CUTANEOUS REACTION AND DESENSITIZATION IN QUININ IDIOSYNCRASY\*

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The purpose of this communication is to add two new cases of idiosyncrasy to quinin to the long list of such instances encountered in the literature, with an allusion to a skin reaction and attempts at desensitization.

CASE 1.—G. V. W., male, chief yeoman, aged 22 years, was admitted to the U. S. Naval Hospital, Washington, D. C., as a case of influenza. His illness pursued a typical course and in two weeks he had recovered completely. During the latter days of his convalescence elixir of iron, quinin and strychnin were prescribed for him in 4 mil doses. Within fifteen minutes after the first dose was administered, the eyes began to smart and itch. There was some photophobia and lacrimation. Soon the face, neck, chest and hands became a "lobster red" color, which rapidly became a generalized erythema. This was attended by an intense pruritus. There was a certain degree of headache, puffiness of the eyelids and muscae volitantes, but no vertigo nor tinnitus aurium were noticed. Some dyspnea and epigastric burning were encountered. The erythema and pruritus completely disappeared in two and one-half hours.

On questioning the patient, it was learned that during childhood quinin was frequently taken for coryzal attacks on which occasions no untoward symptoms occurred. Not until eight years ago was any reaction from this drug noticed, when an attack, similar to the one just described, followed the ingestion of approximately 0.2 gm. of quinin. The second attack occurred one year later, when a similar dose was taken. From this time on until two years ago, the patient on several occasions took tablets containing, in addition to other ingredients, 0.065 gm. of quinin. No ill effects were noticed from these until October, 1917, when, after taking one tablet, a syndrome was caused, characterized by erythema, pruritus, edema, headache, vertigo, tinnitus, muscae volitantes, dyspnea, nausea and vomiting. Since 1917 the patient has not taken quinin in any form until his admission to the Naval Hospital.

He says he can eat eggs, cucumbers, strawberries, tomatoes, buckwheat and all types of sea food with impunity. He never had hay fever or horse asthma. Typhoid or smallpox vaccine did not occasion any undue reaction.

His past, family and personal history reveal no noteworthy features. Physical examination is negative.

CASE 2.—Captain S., U. S. Marine Corps, male, aged 28 years, married was admitted to the U. S. Naval Hospital, Washington, D. C., complaining of tenderness, weakness, loss of weight and stiffness in the legs and thighs. There was no cough and repeated physical examinations and thoracic roentgenograms failed to reveal any tuberculous process. The patient had returned

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on sick leave from eighteen months duty in San Domingo, where, since early in March, 1918, he had experienced three definite attacks of benign tertian malaria. The first two attacks were three months apart—in March and June, 1918. They were clinically typical and responded readily to 1 gm. of quinin sulphate, three times a day. On both occasions absolutely no untoward effects were caused by the quinin, nor had the patient ever had cinchonism prior to this time, despite the fact that he had taken 1 gm. of quinin a day as a prophylactic ten years previously while on an engineering expedition in South America. In December, 1918, a third attack of malaria was experienced. As in the previous two attacks, he had distinct chills, forty-eight hours apart, and the *plasmodium vivax* was found in the blood smear. Quinin therapy was instituted. The first dose, 1 gm. of quinin sulphate, produced no ill effects. The second dose of the same size, given a few hours later, caused a blotchy, diffuse rash, generalized pruritus, headache, tinnitus aurium, muscae volitantes, photophobia, lacrimation, dyspnea, epigastric flushes of heat, nausea and diarrhea. This attack persisted for several hours. Therefore the drug was discontinued for two days and then given subcutaneously, once a day. Each injection was attended by a syndrome similar to the first though milder. Having apparently recovered from malaria, the patient returned to this country.

Except for an attack of amebic dysentery in 1913, his health has always been good. Has never had any hay fever, horse asthma nor any reactions to the various fruits, vegetables, sea food or drugs other than quinin.

It would appear from an analysis of these cases that the hypersensitiveness to quinin was acquired. In neither case could a similar familial tendency be elicited. The clinical manifestations were extremely suggestive of cinchonism, and it was found that neither individual reacted with any of the other common drugs where idiosyncrasies are known to occur. Furthermore, it was found that the tolerance of Case 1 was somewhat less than 0.03 gm. when given by mouth, and that of Case 2 was about 0.25 gm. when given by mouth or intravenously in a 5 per cent. solution. Both men failed to react clinically with the other alkaloids of cinchona, whereas the various salts of quinin produced a reaction in sufficient dosages.

After the method of Boerner,<sup>1</sup> skin reactions were tried in both cases. Two superficial abrasions were made with a sterile needle on the flexor surface of the forearm, about 3 inches apart, after the parts were cleansed with 95 per cent. ethyl alcohol and dried. To one was applied quinin bisulphate (1:10) while the other was left untouched, functioning as a control. We were able to confirm Boerner's findings in that the scarification to which the quinin antigen had been applied showed a marked reaction in both men, while the control merely exhibited the results of the traumatism. The reactions began with an itching, smarting or burning sensation from four to five minutes after application. This was quickly followed by an area of edema on either side of the needle scratch. This edematous area was, as a rule, irregular in outline and reached its height in from fifteen or twenty minutes to one hour. It was surrounded by a bright red halo of erythema, which

1. Boerner, F., Jr.: J. A. M. A. 68:907 (March 24) 1917.

varied from 3 to 5 cm. in diameter. An identical reaction could be produced by the use of the chlorhydrosulphate or dihydrochlorid of quinin in 1:20 dilutions. Control tests, as shown in Figure 1, of salicylic acid (10 per cent.), caffein citrate (10 per cent.), potassium iodid (saturated solution), atropin sulphate (0.5 per cent.) and epinephrin (1:1,000) failed to provoke analogous reactions in either patient.

Later, additional controls were made, using cinchonin sulphate, and cinchonidin sulphate as antigens. No reactions were encountered with these alkaloids of cinchona, whereas the quinin yielded the usual intense response.

Twelve individuals were selected who were known not to be hypersensitive to the drug. All were given as much as 2 gm. of quinin sulphate a day without manifesting any discomfort. The cutaneous tests in all these men were negative. As Boerner indicated, there is reason to believe that the reaction is specific to those who are hypersensitive to quinin, and, also, it has been found that these two patients failed to respond to other idiosyncrasy-producing drugs, even to certain other alkaloids of cinchona.

An attempt was now made to desensitize the patients to quinin. The procedure described by Heran and Saint Girons<sup>2</sup> gave brilliant results in Case 1, while the tolerance in Case 2 was increased from 0.25 to 0.7 gm. The method, briefly, consisted in giving by mouth a "desensitizing dose" of 0.005 gm. with 0.5 gm. of sodium bicarbonate. In one hour and thirty minutes, 0.1 gm. of quinin bisulphate and 0.5 gm. of sodium bicarbonate were ingested in cachets. The "desensitizing dose" remained constant each day, while, in the second dose, the amount of quinin was increased 0.1 gm. each day. The quantity of sodium bicarbonate remained the same. Only one dose was given in any one day. It was found that, except for the "desensitizing dose" on the first day, Case 1 showed no untoward symptoms. At the end of the eleventh day, 2 gm. were being taken without any disagreeable symptoms. Case 2 did not respond so readily, and it was necessary to discontinue the procedure when 0.7 gm. was taken on account of a diarrhea and some visual disturbances. It is of interest to note that the degree of intensity of the skin reaction was in inverse ratio to the amount of quinin ingested without ill effect. In Case 1 the cutaneous reaction gradually became less marked, until on the tenth day it completely disappeared. The reaction in Case 2 became gradually less distinct until 0.7 gm. was given, but when the toxic symptoms manifested themselves there was efflorescence which simulated in intensity that encountered in the initial tests.

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2. Heran and St. Girons: *Montpellier med.* **39**:21, 669, 1917.

Two other methods of desensitization were instituted in Case 2. One was the administration of quinin bisulphate, by mouth, in increasing doses once a day. The initial dose was 0.03 gm. and it was increased by as much each day. The other method consisted in giving a "desensitizing dose" of 0.01 gm. quinin chlorhydrosulphate in 5 mls of sterile water, intravenously, and, after from thirty to forty-five minutes, giving a second dose starting with 0.2 gm. of the same drug and increasing 0.1 gm. a day. By both methods 0.7 gm. could be given with safety, but symptoms appeared if larger quantities were administered.

We are not prepared to offer a theory as to the nature of these reactions in terms of anaphylaxis or allergy. Many investigators, adherent to either the humoral or cellular theories of anaphylaxis, agree that a protein must be associated with its provocation, while others maintain that proteins are not necessary. If it were true that a protein must be involved in the production of anaphylaxis, idiosyncrasies and skin reactions to various alkaloids, which are not proteins, would seek explanation on some other basis. Several authors, notably Zieler<sup>3</sup> and Pöhlmann,<sup>4</sup> have placed these phenomena in the realm of intoxications rather than manifestations of anaphylaxis, basing their conclusions, for the most part, on the inability to produce passive sensitization in animals with the sera of hypersensitive persons. On the other hand, Klaussner<sup>5</sup> and Bruck<sup>6</sup> report passive sensitization in guinea-pigs by injecting the sera of individuals with idiosyncrasies to drugs.

Hans Meyer has evolved a theory that there is an alteration in the calcium content of the tissues, while, on the other hand, Pepper and Krumbhaar<sup>7</sup> deny that there is a deficiency in calcium metabolism in edema and urticaria. Hunt<sup>8</sup> and Lewis<sup>9</sup> have shown that a certain percentage of cases of poison susceptibility can be influenced by diet.

Kolmer,<sup>10</sup> who has had a vast experience with skin reactions, refers to them as "anaphylactic or pseudo-anaphylactic." He states that there is not sufficient data at hand to prove that the mechanism of the local or skin anaphylactic reaction is identical with that of the general or fatal reaction following intravenous injections. He, as well as Longcope,<sup>11</sup> admits that examples of drug anaphylaxis, unless such drugs contain protein substances, offer certain difficulties as to explanation,

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3. Zieler: München. med. Wchnschr. **59**:401, 1641, 1912.

4. Pöhlmann: München. med. Wchnschr. **61**:543, 1914.

5. Klaussner: München. med. Wchnschr. **57**:1451, 1983, 1910; **58**:138, 1911.

6. Bruck: Berl. klin. Wchnschr. **47**:517, 1928, 1910.

7. Pepper, W., and Krumbhaar, E. B.: J. Infect. Dis. **14**:476, 1917.

8. Hunt, R.: U. S. P. H. and M. H. S. Hyg. Lab. Bull. **69**: 1910.

9. Lewis, J. H.: J. A. M. A. **72**:329 (Feb. 1) 1919.

10. Kolmer, J. A.: Infection, Immunity and Spec. Ther., 1917, p. 617; Bull. Johns Hopkins Hosp. **28**:163 (May) 1917.

11. Longscope, W. T.: Am. J. M. Sc. **152**:6125 (Nov.) 1916.

but maintains that a drug may be capable of sensitizing body cells in the same manner, as in the "indirect anaphylaxis" of Richet, or that a new protein compound is formed in the patient's serum to which he may be "actively sensitized."

#### SUMMARY

In the two cases of idiosyncrasy to quinin, the skin test described by Boerner has been found a good index to hypersensitiveness.

2. These cases reacted to various salts of quinin only, failing to respond to cinchonin, cinchonidin, salicylic acid, caffein citrate, potassium iodid, atropin sulphate and epinephrin.

3. A method of desensitization described by Heran and Saint Girons proved efficacious in one case and increased the tolerance in another.

4. The intensity of the cutaneous reaction was found to be in inverse ratio to the degree of desensitization obtained.<sup>12</sup>

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12. Lutz, W.: *Cor.-Bl. f. schweiz. Aerzte* **47**:1601 (Dec. 1) 1917. Sollmann, T.: *J. Pharmacol & Exper. Therap.* **9**:309 (March) 1917. Strickler, A.: *New York M. J.* **104**:198 (July 29) 1916. Zinnser: *Infection and Resistance*, 1919, p. 410.



From above downward the drugs employed were quinin bisulphate (1:10), salicylic acid (10 per cent.), caffein citrate (10 per cent.), potassium iodid (saturated solution), atropin sulphate (0.5 per cent.) and epinephrin (1:1,000).



PROTOZOOLOGIC AND CLINICAL STUDIES ON THE  
TREATMENT OF PROTOZOAL DYSENTERY  
WITH BENZYL BENZOATE

I. A PRELIMINARY REPORT ON EIGHT CASES OF ENDAMEBIC DYSENTERY  
AND ONE CASE OF BACILLARY DYSENTERY TREATED AT  
THE PHILIPPINE GENERAL HOSPITAL

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WITH AN ADDENDUM BY  
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BAGUIO, P. I.

Several months ago the attention of the senior author was attracted by the investigation of the action of the benzyl esters carried out by Macht<sup>1</sup> at Johns Hopkins University. The pharmacologic action of the two esters, benzyl acetate and benzyl benzoate, which formed the subject of Macht's investigations, suggested, as Macht has pointed out, their application to the treatment of the protozoal dysenteries, especially in view of the nontoxic nature of these infections. In his paper, Macht cited a case in which benzyl benzoate was applied, with apparent success, in the treatment of a case of endamebiasis of fifteen years' standing which had been contracted in the Philippine Islands, and this determined us to make a trial of the drug in the wards of the Philippine General Hospital.

Some benzyl benzoate was prepared locally for us and it was found to exert no untoward effects on guinea-pigs when injected pure in moderately heavy doses; but when it was tried out on one or two patients it was found to contain some traces of an impurity which set up a slight degree of gastric irritation and we decided to discontinue its use. Later, we used some of a small batch of the drug prepared at the Bureau of Science, Manila, in three cases. One patient of the three complained of slight nausea; the others took it without experiencing any ill effects.

The senior author entered into correspondence with Dr. Macht, who very kindly had the manufacturers, Messrs Hynson, Westcott & Dunning, of Baltimore, send us a small supply of the pharmaceutically prepared miscible benzyl benzoate, put up in 20 per cent. alcoholic solution. This was used in all of the cases hereinafter recorded except

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1. Macht, David I.: A Pharmacological and Therapeutic Study of Some Benzyl Esters, *J. Pharmacol & Exper. Therap.* **11**:419 (July) 1918.

in the three already mentioned, and in no instance did we observe any untoward effects on the gastrointestinal or urinary tracts, or, indeed, ill effects of any nature.

In starting the work it must be confessed that we had to cope with the prevailing opinion held by many tropical workers, that it is unwise to check the diarrhea in dysentery except through the medium of the specific treatment employed. We are inclined to disapprove of the administration of bismuth or opium in such cases, but we think the objection lies mainly in the treatment of bacillary dysentery which we have only briefly touched on in this series. The protozoal dysenteries are nontoxic, that is to say, so far as the protozoal infection is concerned, and we consider that there is much less danger in checking the diarrhea caused by them than is to be feared from checking the diarrhea of bacillary dysentery, especially through the use of opium. The checking of the diarrhea through the slowing down of peristalsis has been a striking feature of the results we have observed in this series, and in no case has this action been attended by other than good results.

It is our intention to continue these studies. We shall not limit our work to the treatment of endamebiasis, but, as opportunity offers, shall try it in the treatment of the dysenteries caused by *Balantidium coli* and the flagellated protozoa found in the human intestinal tract. The supply of the drug obtained through Dr. Macht was limited, and much of it was saved for use in the treatment of a case of lymphatic leukemia by the same author, in collaboration with Dr. Asuzano, the results of which will be published elsewhere. Our principal object in connection with this short series, was to accustom ourselves to the action of the drug and to outline plans for a more systematic study of its action in the future. In our next paper we shall give a fuller treatment of the action of the drug on the parasites. This paper is mainly a clinical study.

Ten cases were selected in the wards of the hospital and subjected to the treatment to be described. Of these cases, eight were endamebic uncomplicated by infection with *Bacillus dysenteriae*, one was bacteriologically positive for *Bacillus dysenteriae* (Shiga) and showed no evidence of coexisting endamebic infection. The other case was discovered to be one of miliary tuberculosis, in a late stage, with diarrhea. The patient was dropped from the series and died a few days later. To these must be added two cases of endamebiasis treated at the Baguio Hospital by Dr. Asuzano, whose report appears as an addendum to this paper. All the patients left the hospital either free from dysenteric symptoms of any kind, or so markedly improved that they refused to stay longer. How many of these cases represent cures, in

the generally accepted sense, can only be determined by future developments. In no case, except in one of Dr. Asuzano's cases (Case 2), has it been possible to keep the patient under observation. We are reluctant to pronounce a case of endamebiasis "cured" until the stools have been free from trophozoites or cysts for a period of at least thirty days. We incline to the opinion that this period is none too long. Endamebiasis is essentially a chronic disease, as is malaria, and is prone to exhibit surprises to the clinician and microscopist, not dissimilar to syphilis.

Another factor that must be borne in mind in the event that any of these patients applies in the future for treatment of endamebiasis, is that all of them, with the exception of Dr. Asuzano's cases, were individuals belonging to the poorer classes whose ideas of hygiene and sanitation are not even elementary. Unless cases can be controlled with almost military rigor, as may sometimes be done with the inmates of a prison, the worker in the tropics is always uncertain in such cases whether he is dealing with a recrudescence of the original attack or a fresh infection.

In each case we made every effort to secure a correct diagnosis, and we believe that we have been successful in every one of the cases we are presenting. The microscope was used in the determination of the type or types of parasites present and to discover the nature of the cellular exudate carried in the stool. This was checked up, in each instance, where there was the slightest suspicion of a coexisting bacillary infection, by bacteriologic examination by Dr. Walfrido de Leon of the department of pathology and bacteriology, to whom the authors extend their thanks. The customary weight was also placed on the clinical manifestations.

Microscopic diagnosis requires careful interpretation by an experienced worker, but we believe that, in the main, it is more to be relied on than bacteriologic diagnosis under the methods and technic now available to the bacteriologist. We base a diagnosis of endamebiasis only on the finding of the trophozoites of *Endameba dysenterica* as shown by amebae containing ingested erythrocytes, or the discovery of the characteristic quadrinucleated cysts. The character of the exudate carries much weight with us, however. If the cellular elements of the stool are scanty in amount, contain few leukocytes of the polymorphonuclear type and exhibit cells that show evidence of having undergone proteolytic digestion, we suspect endamebiasis, but suspend judgment until we have identified the ameba.

We have found the bacteriologic examination of stools for *Bacillus dysenteriae* a weak reed to lean on. A negative report carries no weight with us. It is our practice to insist that the stool be carried to the

bacteriologist immediately after it has been passed, for experience has shown us, as it has shown many other workers, that delay in the examination of the stools lessens the chances of detecting the bacillus.

The character of the exudate is of value as has been shown by Wenyon and O'Connor,<sup>2</sup> Willmore and Shearman<sup>3</sup> and others, although many of the distinctive features they have pointed out have been known to tropical workers for a long time. We regard as suspicious of bacillary dysentery a stool that is rich in cellular exudate, mostly of a polymorphonuclear nature, one that is strongly indicative of an acute inflammatory process and of toxic necrosis.

Stools of the latter type are often found to contain *Endameba dysenterica*. In such cases it is customary to regard the condition as probably one of mixed bacillary and endamebic infection. Infections of this type are common in the Philippine Islands. But, as time goes on, the conviction is growing on us that such stools are not necessarily indicative of mixed bacillary and endamebic dysentery. We are not in entire accord with authors who hold that endamebic dysentery does not become complicated by invasion of the amebic ulcers in the intestinal wall by bacteria other than *Bacillus dysenteriae* with consequent evidence, in the stools, of an acute inflammatory process, and we lean strongly towards the statement made by Cowan and Miller<sup>4</sup> that they doubt the existence of pure endamebic infection as they are skeptical of the existence of chronic bacillary dysentery. It is this factor that seems to us to inject an element of doubt into the otherwise apparently reliable method of cytodagnosis as employed in the dysenteries.

In addition to the direct examination of samples taken from different parts of the stools, it is our practice to concentrate the stools after a modification of the method of Cropper and Row.<sup>5</sup> This is done when the patient is admitted to determine the extent of associated parasitism present and again when the patient is discharged from the hospital in order to detect the cysts of *Endameba dysenterica*. Table 1 shows the result of the examination in each case on admission.

As a routine measure, all our patients received aperient sulphates. In some instances enemas of potassium permanganate were given to clear out the bowel when the stools were formed. Ipecacuanha, when

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2. Wenyon, C. M., and O'Conner, F. W.: An Inquiry Into Some Problems Affecting the Spread and Incidence of Protozoal Infections of British Troops and Natives in Egypt, etc., J. Roy. Army Med. Corps **28**:151, 1917.

3. Willmore, J. Graham, and Shearman, Cyril H.: On the Differential Diagnosis of the Dysenteries, Lancet **2**:200 (Aug. 17) 1918.

4. Cowan, John M., and Miller, Hugh: Dysentery: a Clinical Study, J. Roy. Army Med. Corps **31**:277, 295, 1918.

5. Cropper, J. W., and Row, R. W. Harold: A Method of Concentrating Endamoeba Cysts in Stools, Lancet **1**:179 (Feb. 3) 1917.

administered, was given in the form of salol coated pills. The dose on each of three successive nights was 180 cg. In acute cases we give 4 cg. of emetin hydrochlorid daily hypodermically. When the acute symptoms subside we reduce the dose to 2 cg. daily. In very severe cases one may employ the combination of ipecac, emetin and benzyl benzoate.

Pending diagnosis, it is our practice, in fulminating dysentery, to administer serum at once. Because of the acute and rapid course that severe bacillary dysentery runs we deem it to the best interests of the patient to give the serum liberally without waiting for the laboratory report. It can do no harm, and may do a great deal of good, for it is the experience of one of us (P. T. L.) that the serum treatment achieves its best results when applied early in the attack. We are cautious in the application of emetin in undetermined dysentery because of its mischievous effects on the heart that may be impaired in bacillary dysentery.

#### MICROSCOPIC FINDINGS ON ADMISSION

Case No.	<i>Endameba dysenterica</i>	<i>Trichomonas intestinalis</i>	<i>Spirochaeta eurygyrata</i>	<i>Ankylostoma duodenale</i>	<i>Trichuris trichiura</i>	<i>Bacillus dysenteriae</i>
67452	+	..	..	+	+	..
67528	+	..	+	..	..	..
67798	..	..	..	+	..	+
67888	+	..	+	..	+	..
68117	+	..	..	+	+	..
68143	+	+	..	+	+	..
68374	+	..	..	+	+	..
68213	+	+	..	..	+	..
68529	+	+	+	+	+	..
Total	8	8	3	7	7	1

The benzyl benzoate we administered in a small amount of cold water three times a day after meals. The doses employed by us varied from 20 to 30 drops of the 20 per cent. alcoholic solution. It will be noted that Dr. Asuzano employed doses of 10 drops only. Notwithstanding this he seems to have secured results which, in the main, seem to be about as good as ours. In our next series we shall endeavor to determine the minimum effective dose as well as the effects of doses even higher than we have employed.

The protocols of our cases are as follows:

#### REPORT OF CASES

CASE 67452.—Male, 21 years of age, admitted to the hospital February 5. On admission the stool showed a scanty cellular exudate containing traces of mucus, erythrocytes and a few leukocytes. It was positive for *Endameba dysenterica*, *Trichuris trichiura* and *ancylostoma duodenale*.

The case presented an acute exacerbation of a chronic endamebiasis of about three months' standing, the original attack having occurred in Novem-

ber, 1918. It lasted about one week. The present attack began three days before admission and was not at first accompanied by severe abdominal pain or tenesmus, but during the early part of his stay in the hospital the patient began to complain of both.

As this was not a case of marked severity, it was determined to treat it with benzyl benzoate alone. On the first night after treatment was started the patient slept well. The treatment was started on February 7, with a dose of 20 drops, three times a day. On the following day the abdominal pain and tenesmus were greatly diminished and the patient passed only two stools. The stools were becoming feculent. February 9, the pain and tenesmus had completely disappeared and the stools were practically normal in consistence. The patient was discharged free from dysenteric symptoms on February 16. His stools had averaged one a day since February 9.

This was undoubtedly a mild case. The stools were becoming formed on February 8, seven days after the onset of the attack. Under the benzyl benzoate treatment the patient showed almost immediate improvement which continued uninterrupted to the day of his discharge.

CASE 67528.—Male, 35 years of age, admitted to the hospital February 8. The stool contained a rather abundant cellular exudate, blood and mucus. The stool was positive for *Endameba dysenterica* and *Spirochaeta eurygyrata*. Bacteriologic examination was negative for *Bacillus dysenteriae*. Nevertheless, the character of the stool was such as to make us strongly suspect bacillary as well as entamebic involvement.

Clinically, the case presented a moderately severe type. The patient had just recovered from an attack of influenza complicated with bronchopneumonia. Six days before admission to the hospital he felt a growing sense of heaviness in the abdomen accompanied by tympanism. This lasted two days. During the following four days the bowel movements became more frequent (ten or more during the twenty-four hours). The movements were accompanied by tenesmus. They were mainly mucoid with a little blood.

On admission, the patient was having four to six movements during the day and from fifteen to twenty at night. The griping and tenesmus had become very severe. The colon was palpable and tender. The patient was very weak and unable to sleep. He was immediately given 20 c.c. of anti-dysenteric serum intramuscularly and was started on benzyl benzoate, 20 drops three times a day. The following day the bowel movements were diminished to four in the twenty-four hours. The night of February 10, the patient slept well. The pain and tenesmus were greatly diminished and the patient passed but two stools. February 11, there was a slight return of the abdominal pain and tenesmus, but both completely disappeared on the following day when the patient was able to be up and around the ward. The stools were well formed by this time and February 16 the patient left for home free from dysenteric symptoms.

It should be noted that this patient received only one dose of anti-dysenteric serum and that further treatment was carried out with benzyl benzoate alone. In view of this, it is questionable if the patient had a coexisting infection with *Bacillus dysenteriae*. The cellular exudate in the stool was, however, strongly suggestive of a concomitant bacterial infection of some kind.

CASE 67888.—Male, 35 years of age, admitted to the hospital February 23. The stool contained blood, pus and mucus. There were numerous active *Endamoeba dysenterica* and Charcot-Leyden crystals. Other parasites present were *Trichuris trichiura*, and *Spirochaeta eurygyrata*. Bacteriologic examination for *Bacillus dysenteriae* was negative on two occasions.

Notwithstanding the presence of pus we are convinced that this was a case of frank endamebiasis of a rather severe type. The patient had been suffering from the disease in a rather mild form, for about one month previous. On the day of admission the stools, which had been averaging about twenty in the twenty-four hours, became more frequent. They were scanty, mucoid and streaked with blood. There was marked tenesmus and abdominal pain. The patient was weak and unable to sleep at night.

Immediately after admission the patient was started on antidyserenteric serum, 20 c.c. intramuscularly, every four hours. There was no improvement in his condition and February 25 he was started on 25 drops of benzyl benzoate, three times a day. The following day the patient passed only three stools as against nine the day before. There was a marked lessening of the abdominal pain and tenesmus and the patient said he felt much better in every way. The improvement continued, although on the following day the endamebae seemed more numerous in the stools. March 2, all pain and discomfort had disappeared and the stools were formed. March 5, there was complete absence of trophozoites and the concentrated stool failed to yield any cysts. The patient was discharged March 6.

CASE 68117.—Male, 55 years of age, was admitted to the hospital March 4. The stool contained much blood, but the cellular exudate was not abundant. *Endamoeba dysenterica* was found as were *Ancylostoma duodenale* and *Trichuris trichiura*.

This case was of interest because of the complete absence of abdominal pain or tenesmus and we deemed it a favorable one on which to observe the effects of benzyl benzoate on peristalsis. The patient said he had suffered from dysentery for twenty-three years, so that the disease may be said to have been thoroughly established. The present attack started February 26, with profuse diarrhea, but with the discharge of neither blood nor mucus. Since the second day of the attack he had experienced difficulty in urination, the urine coming away drop by drop. This condition cleared up later.

On the day of admission the passing of stools was almost constant. The nights of March 5 and 6, ipecacuanha treatment was administered. March 6, benzyl benzoate was started, 30 drops, three times a day. That night the patient slept well for the first time since entering the hospital.

March 8, the general condition of the patient was greatly improved. The effect on peristalsis was very marked for the patient was almost constipated. Later, the stools fell to an average of one a day. The patient was feeling quite well March 11—so well that he insisted on leaving the hospital. His stool was still dysenteric and contained numerous active *Endamoeba dysenterica*. This patient promised to return for treatment on his next attack, which we assured him was probably not far distant.

CASE 68143.—Male, 17 years of age, was admitted to the hospital March 5. The stool contained little cellular exudate, but was laden with erythrocytes and Charcot-Leyden crystals. *Endamoeba dysenterica* was found. Other parasites present were *Trichomonas intestinalis*, *Ancylostoma duodenale* and *Trichuris trichiura*.

On admission the patient complained of abdominal pain and frequent bowel movements containing blood and mucus. The symptoms had developed eight days prior to admission. The patient was able to walk and did not seem particularly sick. There was no palpable mass in the abdomen, but there was slight tenderness on pressure over the ascending colon. The stools were mucoid and streaked with blood and the patient was passing them at the rate of ten to twelve in the twenty-four hours. Defecation was accompanied by pain and tenesmus. Pending diagnosis the patient had received 40 c.c. of antidyserenteric serum intramuscularly on the night of admission.

March 7, the administration of benzyl benzoate, 30 drops, three times a day was started. There was little if any relief from the symptoms the following day, but the patient said he felt much better. March 9 he showed a distinct

Improvement. The tenesmus had diminished in intensity and where the stools had the day before been passed at very frequent intervals, there were only twelve stools in the twenty-four hours. March 11, abdominal pain and tenesmus had disappeared completely and there were only three stools passed that day.

The stools had now become quite normal, and as there was no discomfort of any kind present, the benzyl benzoate was discontinued. Against our strongly expressed advice the patient insisted on leaving the hospital the following day. Unfortunately, his stool could not be obtained for examination before his departure. He was advised to return later for examination, but so far he has failed to put in an appearance. It may be said, however, that the last time his stool was examined microscopically (March 8) neither *Endamoeba* nor *Trichomonas* was found and the stool had lost most of its dysenteric character.

Treatment of this case was carried out wholly with benzyl benzoate, neither ipecacuanha nor its derivatives having been administered.

CASE 68374.—Female, 18 years of age, was admitted to the hospital March 15. The patient's stool contained much mucus and active trophozoites of *Endamoeba dysenterica*. Other parasites present were *Ancylostoma duodenale* and *Trichuris trichiura*.

This case presented a rather severe exacerbation of a chronic endamebiasis dating from 1915. The patient began to exhibit dysenteric symptoms with frequent bowel movements of a bloody and mucoid character, abdominal pain and tenesmus.

March 17, the patient was placed on benzyl benzoate (locally made), 20 drops, three times a day. Two days later the pain and tenesmus had disappeared completely and on that day the patient's bowels moved only once. March 20, the patient failed to move her bowels, and as it was not desired to produce constipation, the benzyl benzoate was withdrawn and the patient was placed on a tonic of iron, quinin and strychnin and Fowler's solution of arsenic. Up to the time of her discharge, April 14, no trophozoites or cysts of *Endamoeba dysenterica* could be found in the stools and the patient was gaining strength every day. She had shown no dysenteric symptoms since March 19. In other words, this patient received benzyl benzoate for three days only and yet apparently was completely cured of the attack. It should be noted in connection with this case that the patient received no anidysenteric treatment whatever, except the benzyl benzoate.

CASE 68529.—Male, 55 years of age, was admitted to the hospital March 21. Examination of the stool on admission showed the presence of active trophozoites of *Endamoeba dysenterica*, *Trichomonas intestinalis* and *Spirochaeta caryogyrata* and the ova of *Ancylostoma duodenale* and *Trichuris trichiura*. The helminthal infections were particularly heavy. By this, it will be seen that the patient was quite extensively parasitized, but such instances of multiple parasitism are not sufficiently rare in the Philippine Islands to excite comment when they do occur. The stool also contained a little pus and mucus.

This was an old chronic case with an acute exacerbation of great severity. The patient had been suffering intermittently from abdominal pains of a vague character since 1908. He would have periodic attacks which lasted about two days and then subsided. It was apparently one of the fairly frequent instances where a chronic or subacute condition has dragged along for a period of years to finally reach a climax in a severe acute attack. The patient was asthenic and emaciated and although the colon was not palpable, there was marked tenderness at the hepatic flexure. The present attack started ten days previous to admission.

The patient was having very frequent bowel movements accompanied by much pain and tenesmus at the time of admission. He was put on ipecac and emetin. For four successive days he received 4 cg. of emetin hydrochlorid hypodermically and on three nights following he received 180 cg. of ipecac each night. The stools diminished in number, but were still passed frequently

and on some days as many as fourteen in twenty-four hours. He gained somewhat in strength, but the pain and tenesmus were undiminished.

At this time the patient was started on the benzyl benzoate (locally made), 20 drops, three times a day. The following day he passed only two stools, but there was no lessening of the pain and tenesmus. The next day following, the pain and tenesmus disappeared completely and the patient had only one bowel movement. The improvement in his general condition was very marked. From that time on the patient never passed more than two stools during the twenty-four hours.

On the fourth day of the administration of the benzyl benzoate the patient began to complain of nausea and the drug was withdrawn with complete disappearance of the trouble. This is the only instance where we observed the slightest ill effects that could be attributed to the benzyl benzoate and it should be noted that the drug administered in his case had been locally prepared and was not the imported pharmaceutical preparation.

During the period when the patient was receiving ipecac and emetin, he was very sick and his condition was at one time extremely unfavorable in outlook. It was found necessary on several occasions to administer camphorated oil and hypodermoclysis. After the benzyl benzoate was withdrawn he received no further antidyenteric treatment until April 12, when a few cysts of *Entamoeba dysenterica* were found in his stool. He was placed on ipecac again for one night and the cysts were absent at the last examination of his stool before he was discharged, April 14. The stool, as in a previous case cited in this paper, was also free from *Trichomonas* but we attach no importance to this because these parasites frequently disappear from the feces for days at a time when the patient is undergoing no treatment whatever, only to reappear later. We doubt the efficacy of any drug which acts through the circulation against lumen dwelling parasites such as *Trichomonas*, unless the drug is eliminated in considerable volume into the lumen at the site of parasitism.

This case afforded an excellent basis for comparison between the effects of ipecacuanha and its alkaloids and benzyl benzoate, for the patient made no real substantial gain until the latter drug was started.

CASE 68213.—Male, 26 years of age, was admitted to the hospital March 9. The microscopic examination of the stool showed the presence of slight cellular exudate, erythrocytes and numerous Charcot-Leyden crystals. Numerous active trophozoites of *Entamoeba dysenterica* were found and there were heavy infections with *Trichomonas intestinalis* and *Trichuris trichiura*. An interesting feature of the *Trichomonas* infection was furnished by the numerous agglomerations of these flagellates seen as the slide was studied.

The case was one of comparatively long standing, the patient complaining that he had suffered from dysenteric symptoms intermittently for the past two years. The present attack was of one month's duration and was accompanied by severe tenesmus.

March 11, the patient had thirteen bowel movements of the characteristic dysenteric type. The following night he was given one dose of 30 drops of the benzyl benzoate. Ten stools had been passed during that day, but March 13 the patient moved his bowels four times only. The supply of benzyl benzoate on the ward had given out and, through a misunderstanding, was not renewed at that time. Ipecac treatment was started the night of March 14. That day the patient had moved his bowels five times, but there was no pain. However, he was very weak. The motions increased in frequency—possibly as a result of the laxative action of ipecac which occurs occasionally, but the increase continued together with a renewal of the tenesmus until March 17, when the patient had eleven movements. The ipecac was stopped and benzyl benzoate (of local preparation), 20 drops, three times a day, was started. There were three movements only on each of the succeeding days, pain and

tenesmus had completely disappeared, but the stools were still dysenteric and contained many endamebae and trichomonads.

The benzyl benzoate was discontinued March 21, at which time the stool was practically formed and contained only slight streaks of blood. The withdrawal of the drug was accompanied in the next four days by a growing frequency in the number of the stools, a return of the pain and tenesmus and the reappearance of blood and mucus in the stool. The night of March 25, ipecac treatment was resumed. The stools gradually decreased in number, but it was not until March 30 that the patient experienced relief from pain and the stools had become formed. The patient was permitted to go home April 2.



Chart of stools passed in Case 68213. Note sudden fall in number of stools following administration of one dose of benzyl benzoate March 12, and rise following administration of ipecac. Note also the sudden fall when benzyl benzoate was again given March 17, and the second rise when the drug was stopped March 21.

This case was one of the most interesting of the series for it seems to show, in a rather striking manner, the more or less positive response in the shape of the amelioration of symptoms each time benzyl is given. There is also a basis for comparison of the action of benzyl benzoate and ipecac. An attempt has been made to illustrate this graphically in the chart.

CASE 67798.—Male, 19 years of age, was admitted to the hospital February 19. The cytology of the stool presented the characteristic picture of

bacillary dysentery, containing necrotic epithelium, polymorphonuclear leukocytes in abundance, blood and mucus. The only animal parasite found was *Ancylostoma duodenale*. Bacteriologically the stool was positive for *Bacillus dysenteriae* (Shiga).

This was a case of acute bacillary dysentery of the most severe type and at the outset we regarded the prognosis as exceedingly grave. The temperature at no time rose above 38.5 C., a condition we have grown to regard as rather an ominous sign in bacillary dysentery.

The onset of the attack was one week previous to admission to the hospital which did not mend matters for the patient. It started as diarrhea with black, foul-smelling stools, slight fever and chilly sensations. The stools became more and more frequent, gradually assuming a typical dysenteric character, then became more scanty in amount and, later, bloody. On admission the bowels were in almost continuous motion.

We approached the treatment of this case with benzyl benzoate with considerable hesitation. The indications for the administration of massive doses of antidyenteric serum were so apparent that treatment was started with 20 c.c. of the serum administered intramuscularly, every four hours. At the same time benzyl benzoate, 25 drops, three times a day, was given. The case ran a stormy course and it was not until February 25 that any change was noted. On that day the abdominal pain and tenesmus were markedly diminished and the patient stated that he felt much better. The following day the abdominal pain and tenesmus were still further relieved, the general condition showed distinct improvement and the stools a tendency to diminish in number. The serum was now administered only twice a day. The improvement continued and March 1 the temperature had fallen to normal, there was little pain or tenesmus and the stools were fewer in number though still numerous. The general condition of the patient was better.

From that time on the patient showed steady improvement. At times the temperature would be intermittent. March 8, the stools were becoming formed and they were fully formed three days later. The patient was then averaging one to two movements in the twenty-four hours.

We are frank to say that we can make no quantitative estimate of the effect of benzyl benzoate in this case. Judged by our experience with similar cases, we feel that the drug helped. We believe that much of the general improvement that became manifest February 25 was due to the benzyl benzoate. Though we observed no bad effects, our inclination is still to employ this drug with considerable caution in the treatment of bacillary dysentery.

#### DISCUSSION

We have employed benzyl benzoate in the treatment of eight cases of endamebic dysentery uncomplicated by bacillary infection and have seen markedly good results in every case. All our cases were of the acute type and varied in severity. We have not as yet tried the action of the drug in chronic cases or in the cases of "carriers" or those persons who discharge abundant cysts without showing symptoms of endamebiasis.

We have, so far, observed no ill effects on the alimentary or excretory tracts following the administration of benzyl benzoate. In no case has the drug unfavorably altered the course of any case. On the contrary, as has been said, its administration has always been accompanied by a marked alleviation of both the objective and subjective symptoms of the disease. It gives the patient much needed rest and

permits him to sleep at night, a most important desideratum in the treatment of dysentery.

Under the administration of the drug the endamebas disappeared from the stools in nearly every case as the general symptoms subsided. Whether this disappearance of the parasites is temporary or permanent remains to be demonstrated by future investigation.

There is ground for belief that benzyl benzoate possesses amebicidal properties. This has been suggested by Macht and Fisher<sup>6</sup> in a series of *in vitro* experiments. While we do not place a high value on such experiments, we consider the point is well worth working on. We can only say that this series of cases does not afford evidence which would tend to establish proof one way or the other.

We believe that in addition to relieving, to a substantial degree, some of the most distressing symptoms which accompany a dysentery attack that, in combination with ipecacuanha or its alkaloids, benzyl benzoate noticeably shortens the term of illness.

It has been shown in some of our cases that benzyl benzoate alone will bring about a complete subsidence of the symptoms of acute endamebic dysentery. Whether these cases are permanently cured or will be subject to relapse must be determined in the future. It is well known that emetin cannot be relied on to cure all cases of chronic endamebiasis and the action of benzyl benzoate adds another factor to the problem of the mechanism of the cure of endamebiasis.

There is certain evidence that when used with care, benzyl benzoate may be employed with advantage in conjunction with serum, in the treatment of bacillary dysentery. It is suggested that it may be of particular value in mixed bacillary and endamebic dysentery where the condition of the heart forbids the use of emetin.

For the present, we consider it safe to state that benzyl benzoate is, to say the very least, a valuable auxiliary to the other forms of anti-amebic treatment, and that it gives real promise of usefulness when employed alone. This is entirely aside from any amebicidal powers it may, in the future, be shown to possess. It is agreeable to take, and if it can be used alone it will be a boon to the patient who suffers from the distressing nausea produced by ipecac.

We believe it is probably unwise in acute cases, especially when a bacillary involvement is present with accompanying toxemia, to push the drug to the point where the patient becomes constipated — a condition that has occurred in two of our cases of uncomplicated endamebiasis.

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6. Macht, David I., and Fisher, E.: *J. Pharmacol. & Exper. Therap.* **11**: 263 (April) 1918.

Benzyl benzoate seems to take the place of morphin in dysentery in that it slows the peristalsis and relieves the pain and tenesmus; but it shows none of the undesirable traits of opium. It is slower in its effects than opium and, of course, obviates the danger of habit formation in a susceptible patient. The sedative action of the drug on the intestinal musculature seems to us to be of preeminent importance. The violent peristalsis is promptly quieted and the intestine is given rest and a chance to carry out the normal reparative processes. It is possible that the spread of the infection is also distinctly limited through the quieting of the gut. Rest for the intestine seems to us to be fully as important as bodily rest for the patient secured by keeping him in bed.

So far as we have observed, benzyl benzoate exerts no effects on any of the intestinal protozoa other than *Endameba dysenterica*, neither were the intestinal helminths encountered affected by it.

#### CONCLUSIONS

It seems evident that benzyl benzoate exerts a definite and favorable influence on the course of endamebic dysentery. The question arises as to how this effect is brought about. Among the points that should be determined in the future are the following:

1. Its action on chronic and "carrier" cases and in hepatic endamebiasis as well as endamebic involvement of the urinary system and other organs.
2. The determination of the minimum effective dose, and the action of larger doses than we have given.
3. Its effects on the hemopoietic system.
4. Has the drug specific amebicidal properties, possibly through the splitting off of one or more of its radicals in metabolism? If such is the case a curative action may be expected.
5. Is the effect more on the host than on the parasite? That is to say, does it have a tendency to restore the normal equilibrium between parasite and host with accompanying subsidence of the acute symptoms and assumption of a state of chronicity, but without sterilization of the patient? Under such circumstances relapse to an acute condition may be expected sooner or later.
6. Does the sedative action of the drug on the intestinal musculature merely limit the spread of the infection and possibly permit some undetermined body defense to regulate the infection?
7. Is there a possibility of synergistic action between benzyl benzoate and ipecacuanha and its alkaloids, or, is it possible that benzyl benzoate tends to make the endameba more sensitive to the action

of ipecac and emetin? In this connection attention is drawn to Case 68313.

In conclusion, we desire to extend our thanks to Dr. Ariston Bautista y Lim, head of the department of medicine on whose service these patients were assigned, for permission to study them, and to Drs. Facundo Esquivel, F. R. Fernandez de Leon and Wenceslao Vitug of the house staff for substantial assistance rendered.

#### APPENDUM

### TWO CASES OF ENDAMEBIC DYSENTERY AT BAGUIO HOSPITAL TREATED WITH BENZYL BENZOATE

M. A. ASUZANO, M.D.

BAGUIO

These two cases of acute endamebic dysentery were treated by me at the Baguio Hospital at the instance of Professor Haughwout, who furnished me with a supply of benzyl benzoate miscible in 20 per cent. alcoholic solution. They are of some interest inasmuch as one of the patients received emetin compounds in addition to the benzyl benzoate, while the other was treated with the benzyl benzoate alone.

The following is a report of my cases:

#### REPORT OF CASES

CASE 1.—C. Y., a Spanish mestiza, 31 years of age, had dysentery six or seven months ago at which time her stool was reported positive for *Endamoeba dysenterica*. Two physicians treated her at that time by both hypodermic and intravenous administration of emetin hydrochlorid. She suffered three relapses. The patient came to Baguio and two days later came down with another acute attack. Her stool contained an abundance of mucus and blood and a large number of actively motile endamebas.

I gave her six injections of emetin, in one-half grain doses, and, she having failed to improve, gave her in all, six grains of emetin bismuthous iodid. Examination of the stool following this treatment, showed numerous cysts of *Endamoeba dysenterica*, but three days later she came down with another acute attack. I continued the treatment with emetin bismuthous iodid, giving her 12 grains in all. About a week after the discontinuance of the drug, she had another acute attack, and, as in the previous instance, had from ten to fourteen bowel movements a day. These were accompanied by intense griping pains in the abdomen, intense burning pain in the region of the rectum, accompanied by distressing tenesmus.

At this period I started her on the benzyl benzoate, 10. drops three times a day. After taking three doses of the benzyl benzoate the number of bowel movements fell to four. The stools still contained mucus, slightly streaked with blood and endamebas. The abdominal pain and distress were by this time markedly diminished. The second day the patient had but one movement of a semisolid nature. Pain in the abdomen had disappeared almost altogether as had the pain in the rectum.

However, the stools still bore traces of mucus and contained few endamebas, so I put her on emetin again, giving her, in all, 2 grains of the hydrochlorid and 6 grains of the emetin bismuthous iodid.

At the end of a week two stool examinations failed to show the presence of blood, mucus or endamebas. Two examinations by the concentration method of Cropper and Row failed to show the presence of cysts.

CASE 2.—J. S., Filipina, 24 years of age, was already under treatment in the hospital for pulmonary tuberculosis. She was in the second stage of that disease. She developed endamebic dysentery, her stool showing an abundance of mucus, blood and active *Endamoeba dysenterica*. She was passing eight to ten stools a day. These were accompanied by distressing gripping pains in the abdomen, burning pain in the rectum and tenesmus. On the second day of the illness I started her on 10 drops of the benzyl benzoate, three times a day. Following the first three doses the daily number of stools fell to two. These were of semi-solid character, but still contained mucus, blood and endamebas. The parasites were very sluggish in their movements. No cysts were found. The pain was much diminished in intensity, but had not disappeared. On the second, third and succeeding days the bowel movements were normal and no endamebas were found either as trophozoites or encysted forms. All pain and distress had disappeared.

#### COMMENT

The first case was the more severe of the two. Treatment included the administration of emetin bismuthous iodid, and later emetin hydrochlorid, but under it little, if any, improvement was noted in the symptoms. Later, emetin hydrochlorid was combined with benzyl benzoate which brought about a complete and speedy subsidence of all the symptoms and the disappearance of the parasites from the stool.

No emetin was given to the second patient. Under treatment with benzyl benzoate the symptoms rapidly disappeared and, with them, the endamebas in both the trophozoite and encysted forms disappeared.

# A STATISTICAL DISCUSSION OF THE RELATIVE EFFICACY OF DIFFERENT METHODS OF TREATING PNEUMONIA \*

RAYMOND PEARL

BALTIMORE

Recently Head<sup>1</sup> contributed an interesting discussion of the results of treating post-influenzal pneumonia by the open as contrasted with the close ward method. The general result apparently was to show that the latter method was greatly superior to the former, as evidenced by the case fatality rates under the two modes of procedure. While the author definitely draws this conclusion and states with confidence that the study of the 1,400 cases he dealt with "points the way to the more successful management of this disease," he also raises a rather obvious point of criticism to the results as they stand, using the following words:

The question at once arises, Is the lowered mortality here shown in favor of the closed ward treatment a real gain in the management of the disease over the open ward method, or are the favorable results only a coincidence, an expression of a lowered mortality arising naturally in the latter part of the epidemic? It has been stated by Abrahams, Hallows and French that the mortality is higher and the disease more severe in the early part of epidemics of influenza complicated by pneumonia.

The problem raised is an interesting one statistically, and one of a sort which continually arises in medical literature. A new method of treatment for a disease is devised and tried in a number of cases with a case fatality rate lower, by a greater or smaller amount, than the case fatality rate which had prevailed under some other mode of treatment. The problem in any such case is this: Is the lowering of the case fatality rate in the new circumstances so great that it cannot reasonably be supposed to have arisen by chance alone? Usually, no adequate evidence on this point is given by the physician, chiefly for the reason that he has no technical knowledge of the proper mathematical tests to apply. The potency of random sampling in bringing about divergences is apparently but little understood outside of professional statistical circles.

As an illustration of the effects of random sampling let us consider a hypothetical case. In any large city, or a state, or indeed, any large population aggregate, the average age at death of persons dying at the same calendar date should be identical for all dates, except for the influence of two factors, viz: (a) chance, or random sampling, and (b) long seasonal waves arising from the fact particularly that rela-

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\* Papers from the Department of Biometry and Vital Statistics, School of Hygiene and Public Health, Johns Hopkins University, No. 6.

1. Head, G. D.: Treatment of Pneumonia, J. A. M. A. **72**:1268 (May 3) 1919.

tively more infants die in hot summer weather than in the colder seasons of the year. In any short period, say ten consecutive days, the second factor (b) would not operate, and we should expect the persons dying on each of these consecutive ten days to show the same average age, except for the fluctuations due to chance alone. How considerable these fluctuations may be is shown in Table 1, which gives the number of deaths and the average age at death of those dying during ten consecutive days in 1916 in Baltimore.<sup>2</sup>

TABLE 1.—MEAN AGE AT DEATH OF THOSE DYING IN THE STATED DAYS IN BALTIMORE

Date	Number of Deaths	Mean Age at Death in Years
Jan. 13, 1916.....	31	30.16
14.....	40	43.80
15.....	27	40.59
16.....	48	48.21
17.....	32	48.34
18.....	41	51.90
19.....	39	46.82
20.....	31	52.39
21.....	39	51.62
22.....	57	39.40
Total for the year.....	10,668	39.83

Here we have a fluctuation in the average, based on samples of from thirty to fifty individuals, amounting to more than twenty-two years, arising from random sampling alone. Such an illustration emphasizes the fact that before conclusions can safely be drawn from differences between numbers it is necessary to know something about the "probable errors" of those numbers.

The particular theorem in probability which is applicable in problems of the type exemplified in Head's paper referred to above was first set forth by Pearson.<sup>3</sup> I have recently discussed this subject further.<sup>4</sup>

Let it be supposed that a first sample of  $n = p + q$  be drawn from the population,  $p$  denoting the number of times the event dealt with occurs in the  $n$  trials, and  $q$  the number of times it fails.

Write

$$\bar{p} = \frac{p}{n}, \quad \bar{q} = \frac{q}{n},$$

whence of course

$$\bar{p} + \bar{q} = 1.$$

We then have for the chief constants of the error distribution for a second sample, of magnitude  $m$ , drawn from the same population the following values:

2. I am deeply indebted to Dr. John H. Blake, Commissioner of Health, and Dr. W. T. Howard, Assistant Commissioner of Health of Baltimore, for kindly allowing me the use of the records of the Health Department for the study of this and other problems now being investigated in this laboratory.

3. Pearson, K.: *Phil. Mag.*, March, 1907, p. 365.

4. Pearl, R.: *Amer. Nat.* **51**:144, 1917.

$$\text{Mean}^2 = m\bar{p} + \frac{m}{n+2} (\bar{q} - \bar{p}), \quad (\text{i})$$

$$\text{Mode} = \text{the integral portion of } m\bar{p} + \bar{p} \quad (\text{ii})$$

$$\text{Standard deviation} = \left\{ m \left[ \bar{p} + \frac{\bar{q} - \bar{p}}{n+2} \right] \left[ \bar{q} - \frac{\bar{q} - \bar{p}}{n+2} \right] \left[ 1 + \frac{m-1}{n+3} \right] \right\}^{1/2} \quad (\text{iii})$$

These values are entirely general and independent of the values of  $n$ ,  $m$ ,  $p$  and  $q$ . Under certain circumstances, as when  $n$  is very large as compared with  $m$ , and neither  $p$  nor  $q$  is very small, (i) and (iii) are obviously capable of being put in much simpler form and still giving a sufficiently close approximation to the true result.

Let us now apply this theorem to the data given by Head.<sup>1</sup> From the figures he gives we may state the problem in these terms: If under the open ward treatment, out of a sample of 966 patients with acute pneumonia 135 died, what would be the probable number to die in a second sample of 435 acute pneumonia patients from the same population, given the same treatment?

We have here, in our mathematical notation

$$\begin{aligned} n &= 966 \\ m &= 435 \\ p &= 135 \\ q &= 831 \\ \bar{p} &= \frac{135}{966} = .1397 \quad \bar{q} = \frac{831}{966} = .8603 \end{aligned}$$

Whence from (i) and (ii) we readily deduce

$$\begin{aligned} \text{Mean deaths expected in second sample} &= 61.12 \pm .28 \\ \text{Modal, or most probable number of deaths in second sample} &= 61 \\ \text{Standard deviation} &= 8.72 \end{aligned}$$

But the actually observed number of deaths in the second sample, under the close ward treatment, was fourteen instead of sixty-one. Hence we may safely conclude that under the close ward treatment significantly fewer persons died than would have been expected to die on the basis of chance, if the same force of mortality had prevailed in the latter period as did in the former.

But can it be assumed that the same force of mortality was impinging, and its results were mitigated only by the new method of treatment? As we have seen, Head himself expresses some doubt on this point, and surely no safe conclusion as to the merits of the treatment can be drawn until this point is settled. In order to settle it we have used data from a comparable outbreak of post-influenzal pneumonia where the same treatment was followed throughout the outbreak. Would there be in such a case a falling off of the case-fatality rate in the latter part of the epidemic corresponding entirely or in some degree to that observed by Head? Through the kindness of

5. From the origin at the lower range end, or  $r=0$ .

Dr. Eugene L. Opie, to whom I wish to express my indebtedness, I am able to present data of this sort for the Camp Pike epidemic.

Table 2 gives the cases and deaths in the Camp Pike epidemic. The cases have already been published by Opie<sup>7</sup> *et al.* The deaths by days he kindly furnished me in manuscript.

TABLE 2.—CASES AND DEATHS OF PNEUMONIA AT CAMP PIKE, ARK., FROM SEPT. 1 TO OCT. 31, 1918

Day September	Cases of Pneumonia	Deaths from Pneumonia	Day October	Cases of Pneumonia	Deaths from Pneumonia
1	1	0	1	126	16
2	3	0	2	142	11
3	2	0	3	113	20
4	1	0	4	129	32
5	3	0	5	86	20
6	3	1	6	89	22
7	4	0	7	93	29
8	3	0	8	76	30
9	1	0	9	42	30
10	3	0	10	66	28
11	4	0	11	54	32
12	1	0	12	34	20
13	4	0	13	15	18
14	7	1	14	13	13
15	10	0	15	9	13
16	10	0	16	19	11
17	7	0	17	8	8
18	5	3	18	8	8
19	11	..	19	9	7
20	12	..	20	11	1
21	10	1	21	5	5
22	13	1	22	6	1
23	15	5	23	11	5
24	13	3	24	5	8
25	25	3	25	7	2
26	16	0	26	3	0
27	23	0	27	1	5
28	30	3	28	1	1
29	40	11	29	3	1
30	35	11	30	0	1
			31	0	0
Totals.....				1,499	441

In order to treat these data in a way comparable to the others, it is necessary to divide the epidemic at a corresponding point. In the Camp Wheeler epidemic (Head's data) the change in treatment occurred after 966 out of 1,401 cases had occurred. The same stage of the Camp Pike epidemic was reached  $\frac{966}{1,401} \times 1,499 = 1,034$  cases had occurred. The nearest date to this point, as can be determined by summing the "case" columns of Table 2, is October 6. At the end of that day 1,000 cases of pneumonia had occurred in the Camp Pike epidemic. We may then take through October 6 as the first phase of the Camp Pike epidemic, so far as concerns cases, this phase corresponding to the "open ward" period of the Camp Wheeler data. We have next to consider the deaths which belong to these 1,000 cases occurring prior to the end of October 6. In general, it appears from the data in hand that there was, on the average, a lag of about eight

7. Opie, E. L., Freeman, A. W., Blake, F. G., Small, J. C., and Rivers, T. M.: J. A. M. A. 72:556 (Feb. 22) 1919.

days between case and death curves in the epidemic of post-influenzal pneumonia in camps. Accepting this figure, as in accord to a first degree of approximation at least, with the facts, we have October 14 as the date for dividing the Camp Pike death curve into two portions, which will correspond approximately to the two different treatment moieties of the Camp Wheeler data.

In the same notation as before we have for Camp Pike:

Cases of pneumonia through October 6 =  $n = 1,000$

Deaths from pneumonia through October 14 =  $p = 364$ , whence  $q = 636$ , and  $\bar{p} = .364$ , and  $\bar{q} = .636$

Cases of pneumonia beginning October 7 and going to end of the epidemic =  $m = 499$

The problem then may be stated in this way: If, with no change of treatment, 364 patients died out of a sample of 1,000, what is the probable number of deaths in a second sample of 499 cases? By the same method as before the data give

Mean deaths expected in second sample =  $18.77 \pm .40$

Modal, or most probable number of deaths in second sample = 182

Standard deviation = 13.15

Now, the actual number of deaths in the last 499 cases of the Camp Pike epidemic was only seventy-seven instead of the expected 182. But there had been no change in method of treatment. Hence, it is clear that the statement of Abrahams, Hallows and French, quoted from Head at the beginning of this paper, is true. Fewer deaths in proportion to cases occur in the later as compared with the earlier portion of these epidemic outbreaks, quite without change of treatment.

This result obviously tends to cast reasonable doubt on the efficacy of the close ward as compared with the open ward treatment of these epidemic pneumonias. It is necessary, however, to make a further quantitative comparison before drawing any final conclusion. In the second sample (latter part) from the Camp Pike epidemic the actual deaths formed 42 per cent. of the deaths expected on the basis of chance from the results shown in the first sample from the same epidemic ( $\frac{77 \times 100}{182} = 42$  per cent.). In the Camp Wheeler epidemic (Head's data) the actual deaths under the close ward treatment formed only 23 per cent. of the deaths expected on the basis of chance from the results shown in the first sample from the same epidemic, under the open ward treatment ( $\frac{14 \times 100}{61} = 23$  per cent.).

This result gives the significant comparison. The whole matter may be summarized in this way. While it is true that the case fatality rate tends under a constant form of treatment to be markedly lower in the later portions of epidemic outbreaks of pneumonia, nevertheless Head's data show, when given proper mathematical analysis, that under the close ward treatment only about half (23 per cent. versus

42 per cent.) as many deaths occurred relatively in the latter part of the epidemic as would have occurred under the open ward method of treatment, after making allowance for the normally diminishing case fatality rate of later portions of the epidemic. To that degree, then, Head's conclusions are justified, and obviously constitute an important contribution to the sum of medical knowledge regarding the proper treatment of pneumonia.

#### COMMENT

The first purpose of this paper is to find out, by appropriate mathematical treatment of the data, the real truth as to the relative merits of two methods of treating epidemic pneumonia. Because of the lack of such analysis the results as originally published by Head, comparing the open ward and close ward treatments, were scientifically inconclusive.

The second purpose of the paper is to illustrate by a concrete example, not only the importance, but indeed the absolute necessity of mathematical tests of the validity of results and conclusions, if medicine is ever to measure up to the standards of scientific logic and accuracy which prevail in some, at least, of the other branches of biologic and physical science. Many, indeed most, of the problems of practical medicine in a broad sense are either essentially statistical problems, or their statistical phase is a vitally important one in reaching correct conclusions. The medical man is thoroughly familiar with the necessity for clinical and laboratory tests. Only in rare instances does he realize the necessity of applying to his results before drawing conclusions from them, whether for purposes of publication or practice, a proper test for the magnitude of the probable errors arising from random sampling. It is a commonplace of medical literature to find the most positive and sweeping conclusions drawn from a sample so meager as to make scientifically sound conclusions of any sort utterly impossible. It is not too much to say that the investigator in the field of medicine should be as familiar with the probable error test as he is with the Wassermann test.

#### SUMMARY

In this paper it is shown that in deciding as to the merits of different methods of treatment of a disease it is necessary to take account of the probable errors arising from random sampling. In the case of Head's results on the pneumonia epidemic in Camp Wheeler the reduction in the fatality rate following the institution of the close ward treatment is shown to be only in part a result of the treatment, the remainder being the normal reduction in the case-fatality rate in the later portion of epidemics.

## THE BASAL METABOLISM IN HYPOTHYROIDISM \*

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In connection with an extended study of the basal metabolism in exophthalmic goiter, which has been in progress since 1914 and on which a preliminary report was published in the spring of 1917,<sup>1</sup> opportunities arose to study several cases of hypothyroidism.

The present series comprises observations on six patients and includes practically every condition clinically associated with hypothyroidism, namely, myxedema, cretinism, cachexia strumipriva, and cancer of the thyroid gland. The effect of thyroid administration on the basal metabolism has been studied over a long period of time in the case of a cretin and in one patient with myxedema; also in a patient with cachexia strumipriva, before, during and after the appearance of hypothyroid symptoms.

The methods employed have been fully described in earlier papers,<sup>2</sup> and consisted briefly in the determination of the gas exchange of the recumbent subject while in the postabsorptive condition by means of the small Benedict apparatus and the calculation of the heat production therefrom.

The metabolism data are all shown in the table, the figures for any one day being the average of at least two and usually of three ten minute periods on the Benedict apparatus. The heat production is calculated from the oxygen absorption and the respiratory quotient obtained, except in a few instances where oxygen alone was determined, in which case a respiratory quotient of 0.82 has been assumed.

The body surface figures are obtained from DuBois' height-weight chart,<sup>3</sup> and the figures for standard basal metabolism are those adopted by the workers at the Russell Sage Institute of Pathology.<sup>4</sup>

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\* From the Medical Service of the Massachusetts General Hospital, aided in part by a grant from the Proctor Fund, Harvard Medical School.

1. Means, J. H. and Aub, J. C.: Study of Exophthalmic Goiter from the point of view of the Basal Metabolism, *J. A. M. A.*, **69**: 33 (July 7), 1917.

2. Means, J. H.: Studies of the Basal Metabolism in Obesity and Pituitary Disease, *J. Med. Res.* **32**:121, 1915. Means J. H.: Studies of the Basal Metabolism in Disease and their Importance in Clinical Medicine. Boston M. & S. J. **174**:864 (June 15), 1916.

3. DuBois, D., and DuBois, E. F.: Clinical Calorimetry, X, *Arch. Int. Med.* **17**: Part ii, 863 (June), 1916.

4. Aub, J. C., and DuBois, E. F.: Clinical Calorimetry, XIX, *Arch. Int. Med.* **19**: 823 (May), 1917.

CASE REPORTS<sup>5</sup>

CASE 1.—*Myxedema*. (Lab. No. 2, Hospital No. 198463, W. M.) Mrs. D., a housewife, 57 years of age, first came under our observation October 1, 1914. Six years previously she had been in the hospital with a history of dyspnea and edema of the face and legs, present for four years. A diagnosis of anasarca and ascites was made at that time, but, nevertheless, myxedema was suspected and she was told to take thyroid extract but did not do so.

September 30, 1914, she again entered the hospital. The same symptoms had persisted during the interval and had increased in severity. She was getting dull mentally, so her relatives said, and complained frequently of feeling chilly. Physical examination showed the typical picture of myxedema. The subcutaneous tissue was thickened throughout; there was marked puffiness about the eyes, and fat pads about the neck and shoulders. The skin was dry and scaly, the hair sparse and quite coarse and brittle. The physical examination in other respects was not remarkable. The blood pressure, the blood picture and cell counts, and the urine examination were all quite normal. The Wassermann (blood) was negative and roentgenogram of the head showed a normal sella turcica.

October 2, 1914.—Basal metabolism 28 per cent. below normal.

October 5, 1914.—Second metabolism determination 33 per cent. below normal. Following this thyroid administration was begun. Thyroid extract, 4½ grains, was given on this date.

October 7 and 8, 1914.—Thyroid extract, grains 6, daily.

October 9, 1914.—Thyroid extract was increased to grains 7½ daily.

October 11, 1914.—Basal metabolism, 9 per cent. below normal.

October 18, 1914.—Discharged on thyroid extract, grains 7½, daily.

November 2, 1914.—Readmitted to hospital. Since discharge she had taken thyroid extract, grains 7½, daily. She had been troubled with anorexia, nausea and vomiting. She was emaciated and her breath had a slight odor of acetone. The myxedematous appearance was gone.

November 3, 1914.—The electrocardiogram showed a normal rhythm, and an upright "T" wave in Lead II. There was indication also of left ventricular preponderance.

November 4, 1914.—Basal metabolism was 3 per cent. above normal. Thyroid extract was discontinued.

November 7, 1914.—Vomiting had ceased, and she appeared to be well. Discharged on thyroid extract, grains 1½, per day.

October 31, 1916.—The patient called at the hospital in response to a letter. She had been taking thyroid extract, grains 1½, every day since November 7, 1914, except for one or two short periods when her supply of tablets was exhausted. She has felt very well and was alert mentally. Her appetite was good. She perspired like a normal individual. She was not chilly. Her hair fell out and her skin desquamated two years ago, but now she has normal skin and a good growth of new hair. She was ordered to take thyroid extract, 1½ grains per day half the time and 3 grains per day the remainder of the time.

January 15, 1917.—She came to the hospital for a metabolism determination. This showed a result 11 per cent. above the normal. Since her last visit she had been taking thyroid extract, grains 3, per day about three fourths of the time, and 1½ grains per day about one fourth the time. She felt and looked well. There were no symptoms of either hypothyroidism or hyperthyroidism. Since her metabolism was higher than it ever had been before she was directed to reduce the dose of thyroid extract to 1½ grains per day.

5. One observation on Mrs. D. was published by Means, J. H.: *Proc. Soc. Exp. Biol. & Med.* **12**: 13, 1914, and four by Means, J. H.: *Boston M. & S. J.* **174**: 864 (June 15), 1916, where she was designated Case 10. Also the three observations on Mrs. R. were given in the last mentioned paper, Case 11, but in an incomplete form.

METABOLISM DATA OBTAINED IN CASES OF MYXEDEMA, CRETINISM AND CACHEXIA STRUMIPRIVA

Date	Age	Height, Cm.	Weight, Kg.	Body Surface (Du Bois Height- Weight Chart) S. M.	Oxygen, C.c. per Min.	Carbon Dioxide, C.c. per Min.	Respira- tory Quo- tient	Pulse	Total Calories per Hour	Calories per Square Meter per Hour	Normal Stan- dard Calories per Sq. M. per Hour	Vari- ation, per Cent.	Remarks
<b>Mrs. D. (Case 1)</b> Myxedema													
10/ 2/14	57	153.0	67.0	1.65	144	115	0.80	58	41.5	25.1	35.0	-28	Treatment not begun. Typical myx- edema
10/ 5/14	57	153.0	67.0	1.65	130	119	0.91	63	38.5	23.3	35.0	-33	No thyroid yet
10/11/14	57	153.0	64.5	1.62	182	131	0.72	69	51.4	31.7	35.0	- 9	Total of 36 grains of thyroid extract since last observation
11/ 4/14	57	153.0	59.0	1.56	199	148	0.74	65	56.4	36.1	35.0	+ 3	On thyroid extract, 7½ grains daily since last observation. Myxede- matous appearance gone
1/15/17	59	152.5	68.5	1.66	225	180	0.80	80	64.8	39.0	35.0	+11	Until Oct. 31, 1916, took thyroid ex- tract, 1½ grains daily. Since then 3 grains daily three fourths of the time, and 1½ grains daily the rest
3/25/19	61	151.0	72.5	1.68	169	Not deter- mined	0.82 As- sumed	54	48.9	29.1	34.0	-14	Since last observation has been taking thyroid extract, 1½ grains per day, steadily. Skin dry but mentally alert
<b>Miss L. (Case 2)</b> Cretin													
2/14/17	20	137.2	39.5	1.21	126	163	0.82	95	36.5	30.1	37.0	-19	Treatment not begun. Typical cretin- ism
2/23/17	20	137.3	39.5	1.21	118	103	0.87	80	34.6	28.6	37.0	-23	No thyroid yet
2/27/17	20	137.2	39.2	1.20	146	121	0.83	87	42.3	35.3	37.0	- 5	Total of 12 grains of thyroid extract since last observation
3/ 2/17	20	137.2	39.6	1.21	155	128	0.83	98	45.0	37.2	37.0	+ 1	Total of 13.5 grains of thyroid ex- tract since last observation
3/ 7/17	20	137.2	37.9	1.19	164	125	0.76	92	46.8	39.3	37.0	+ 6	On thyroid extract, 4½ grains daily since last observation
3/16/17	20	137.5	38.6	1.20	159	119	0.75	87	45.2	37.7	37.0	+ 2	On thyroid extract, 1½ grains daily since last observation. Brighter
4/24/17	20	138.0	35.9	1.17	178	147	0.83	81	51.6	44.1	37.0	+19	On thyroid extract, 1½ grains daily since last observation. Skin no longer dry
10/ 4/17	20	138.0	39.5	1.22	173	135	0.78	88	49.6	40.7	37.0	+10	On thyroid extract, 1½ grains daily since last observation
3/24/19	22	139.5	42.0	1.26	144	Not deter- mined	0.82 As- sumed	67	41.6	33.0	37.0	-11	Took thyroid extract, 1½ grains daily, until June, 1918. None since

Miss N. (Case 3) Cachexia strumipriva	2/17/16	36	167.0	52.0	1.57	175	116	0.66	72	49.2	31.3	36.5	-14	Hemithyroidectomy Dec. 28, 1915. Second operation Feb. 1, 1916. No appearance of myxedema yet. Became myxedematous since last ob- servation. Taken 24 grains of thy- roid extract in last eight days. On thyroid extract, 3 grains daily, since last observation. Myxede- matous appearance gone
	5/ 5/16	36	167.0	60.0	1.67	177	153	0.86	71	51.8	31.0	36.5	-15	
	5/29/16	36	167.0	61.3	1.69	224	104	0.73	70	63.4	37.5	36.5	+ 3	
Mrs. R. (Case 4) Myxedema	11/13/14	41	160.5	60.0	1.63	180	137	0.76	75	51.3	31.4	36.0	-13	Treatment not begun. Typical myx- edema No thyroid yet
	11/14/14	41	160.5	60.0	1.63	151	125	0.83	69	43.8	26.9	36.0	-25	
	11/23/14	41	160.5	Lost	1.63	171	139	0.81	82	49.4	36.5	36.0	-16	
Mrs. G. (Case 5) Myxedema	6/28/16	63	162.7	67.0	1.72	167	133	0.80	72	48.1	29.0	34.0	-18	Treatment not begun. Mild grade of myxedema
Mr. B. (Case 6) Carcinoma of thyroid	10/31/16	56	175.3	69.0	1.54	189	166	0.88	72	55.6	30.2	37.5	-19	Before operation Partial thyroidectomy Nov. 4, 1916
	12/21/16	56	175.3	65.0	1.80	193	Not ob- tained	0.82 as- sumed	68	55.9	31.0	37.5	-17	

March 25, 1919.—She again called at the hospital in response to a letter. She had been taking thyroid extract,  $1\frac{1}{2}$  grains per day, ever since her last visit two years ago. Her general health had been good in the interim. She was gaining in weight. Her skin was somewhat dry but her expression was alert and she was bright mentally. Her basal metabolism was found to be 14 per cent. below the normal, so she was directed to increase the dose of thyroid extract to grains 3 every day for a week and on alternate weeks  $1\frac{1}{2}$  grains per day.

April 22, 1919.—She called to have her photograph taken (Fig. 1). She has been carrying out directions and feels entirely well.



Fig. 1.—Case 1. A. was taken in October, 1914, before treatment was begun. B. was taken in April, 1919, after four and one-half years of treatment.

**CASE 2.—Cretinism.** (Lab. No. 142. Hospital No. 213318, E. M.) Miss L., a dwarf, 20 years of age, first entered the hospital February 13, 1917. Her family history was unimportant.

*Personal history.*—She had always been well but never was very strong. When 8 years of age she began to grow obese. When 10 years of age she had reached her present height. She has always felt the cold and been fond of many covers at night. She has always perspired very little. She gave a history of having had a complete set of milk teeth, followed by four upper and eight lower permanent teeth; the remainder of her present teeth are of the first set.

She went to school first when 5 years of age, and graduated from high school at 20. She had menstruated normally since 13 years of age.

*Examination.*—Physical examination showed a short, solidly built woman, whose short stature was not due to a relative shortening of either trunk or legs. Her arms reached midway between the hip and the knee. She was mentally bright but not vivacious. Her hands and feet were of normal shape and small in proportion to her height. Her head was square with wide face and broad cheek bones. The bridge of the nose was depressed and the forehead broad. The eyes had a slightly mongolian outline. The teeth were in fair condition, the posterior ones being small and poorly developed, the anterior ones being fairly widely spaced. The neck was short with marked double chin; the thyroid was not palpable. At the sides of the neck and over the more

prominent vertebrae there were marked pads of fat. The hair was dry and brittle, but not coarse. There was no axillary hair; the pubic hair was scanty and her eyebrows were sparse. Her skin was dry and somewhat harsh, particularly over the extremities. The breasts were fairly developed, about like those of a girl at puberty. The abdomen was fat and protuberant, especially below the umbilicus. In other respects the physical examination was negative.

The blood and urine examinations were not remarkable and the Wassermann (blood) was negative. Roentgenograms of the skull showed a normal sella turcica, those of the wrists and hands showed the lower epiphysis of the radius and ulna, and all those of the metacarpals and phalanges ununited.

February 14, 1917.—Basal metabolism was 19 per cent. below normal. The electrocardiogram showed normal rhythm and an inverted "T" wave.

February 23, 1917.—Basal metabolism was 23 per cent. below normal. Following the determination, thyroid extract, grains 3 per day, was started.

February 27, 1917.—Basal metabolism was only 5 per cent below normal. Thyroid extract was increased to grains  $4\frac{1}{2}$  per day.

March 2, 1917.—Basal metabolism was 1 per cent. above normal.

March 7, 1917.—She has been on thyroid extract, grains  $4\frac{1}{2}$ , since the last observation. Basal metabolism was 6 per cent. above normal. No symptoms of hyperthyroidism were present but she has lost a little weight. The electrocardiogram showed a normal rhythm and the "T" wave was no longer inverted. It was merely flat. Thyroid extract was reduced to  $1\frac{1}{2}$  grains per day.

March 14, 1917.—The electrocardiogram showed a normal rhythm and a "T" wave 2 mm. high.

March 16, 1917.—Basal metabolism was 2 per cent. above normal. She was much brighter. Discharged on thyroid extract,  $1\frac{1}{2}$  grains per day.

April 24, 1917.—She called at the hospital for observation. Basal metabolism was 19 per cent. above normal. The electrocardiogram was as on March 14. Her eyes were brighter and the pads of fat on her back were gone. Her hands were moist and warm.

October 4, 1917.—Patient called again at the hospital for observation. She had been taking thyroid extract,  $1\frac{1}{2}$  grains per day, since last observation. The basal metabolism was 10 per cent. above normal.

March 24, 1919.—Patient came to the hospital in response to a letter. She continued to take thyroid extract,  $1\frac{1}{2}$  grains per day, until June, 1918. Then her supply of tablets was exhausted and she had taken none since. She felt quite well, was living at home and doing housework. She was bright, and alert mentally. Her appearance was, however, not very different from what it was when she first came under observation; her hair was dry and brittle, but not falling out; the skin was dry but there was some moisture in the palms of the hands. She had menstruated normally since her last visit. She had increased in height by 2.3 cm. since the time when thyroid therapy was first started. Her basal metabolism was 11 per cent. below normal, therefore she was told to take thyroid extract again,  $1\frac{1}{2}$  grains daily.

CASE 3.—*Cachexia Strumipriva*.—(Lab. No. 54. Hospital No. 208010, W. S.) Miss N., a graduate nurse, 36 years of age, first came under our observation February 16, 1916. She had previously been a patient in the hospital and had had two operations on the thyroid gland. She was first admitted to the ward December 7, 1915.

*Previous history*.—From the time she began to menstruate at 14 years of age she had noted some slight fullness in the region of the thyroid. This remained stationary and was not accompanied by other symptoms until a week before her entry into the hospital, at which time she found that her neck was increasing in size and was tender to touch. For three days she had been very depressed and nervous.

*Examination.*—Physical examination showed the thyroid considerably enlarged, somewhat more on the left side than on the right. It was slightly tender. Over the right lobe a musical hum was heard, which was accentuated during systole. In other respects the physical examination was negative and none of the usual signs or symptoms of hyperthyroidism were present. The Wassermann test was negative. The urine showed a moderate amount of albumen and a few casts.

She remained in the medical wards for a time, with an irregular, septic type of temperature curve, and a white count varying between ten and fourteen thousand. It was finally decided to resort to surgery.

*Operation.*—December 28, 1915.—Operation under gas and oxygen by Dr. G. W. W. Brewster. The right lobe of the thyroid was exposed and resected, a small bit of normal gland being left at the superior border. The lobe was found to be enlarged and hard and did not bleed when incised. The patient stood the operation well.

*Pathologic Report.*—The removed tissue was examined. It consisted of a portion of two lobes, the largest 7x2.5 cm., the smaller 2x4 cm. The surface was smooth, firm, and hard. Section was white with small, reddish brown areas. Microscopic examination showed a round cell infiltration about the follicles, with atrophy. In some places the remnants seem as masses of rather large, degenerated cells; in other places with remnants of colloid and occasional giant cells. The anatomic diagnosis was thyroiditis.

She continued to run a septic temperature and was not by any means cured.

*Second operation.*—February 1, 1916, a second operation was performed under gas and oxygen anesthesia by Dr. G. W. W. Brewster. The left lobe of the thyroid was exposed. It was found to be enlarged and smooth, very firm and whitish in color. About six sevenths of this lobe was resected. Small bits of normal looking thyroid tissue were left at the isthmus and attached to the posterior wall of the capsule. The patient made a good recovery from the operation.

*Pathologic Report.*—This lobe measured 8x4.5x4 cm. One surface was irregular. On section the tissue was firm, yellowish gray in color, with small areas of yellowish softening. Microscopic examination showed the tissue between the follicles to be thickened, infiltrated with round cells and in places containing large multinucleated bodies. The follicles in many places were atrophied and in others they contained a little detritus. The anatomic diagnosis was chronic thyroiditis.

February 17, 1916.—The patient made an uneventful operative recovery. On this date the basal metabolism was 14 per cent. below normal, but she had not yet developed any clinical manifestations of hypothyroidism.

March 6, 1916.—Patient was discharged from the hospital apparently in good health.

April 24, 1916.—She was again admitted to the hospital with the story that three weeks previously she had begun to get some puffiness of the face and hands. She also began to feel lazy and dull and her skin became dry.

Physical examination showed the typical picture of myxedema. She was mentally sluggish, her skin was dry and harsh. Her tongue was thickened and her face and hands were puffy. Her hair was not altered particularly. There had been no irregularities in her catamenia. She had gained twenty-five pounds in weight since her second operation.

April 27, 1916.—She started on thyroid extract, 1½ grains per day.

April 30, 1916.—Thyroid extract was increased to 3 grains per day.

May 2, 1916.—Thyroid extract was increased to 4½ grains per day.

May 5, 1916.—Basal metabolism was 15 per cent. below normal.

May 9, 1916.—Patient was much brighter; myxedematous appearance was less marked. Discharged on thyroid extract, 3 grains per day.

May 29, 1916.—She called at the hospital for observation. She had been taking thyroid extract, 3 grains per day, since her discharge. Her condition was very much better. The myxedematous appearance was quite gone. The skin was moist and she was bright and alert mentally. The only evidence of hypothyroidism was that her hair was somewhat coarse, more so in fact than when she was last seen. The basal metabolism was 3 per cent. above normal.

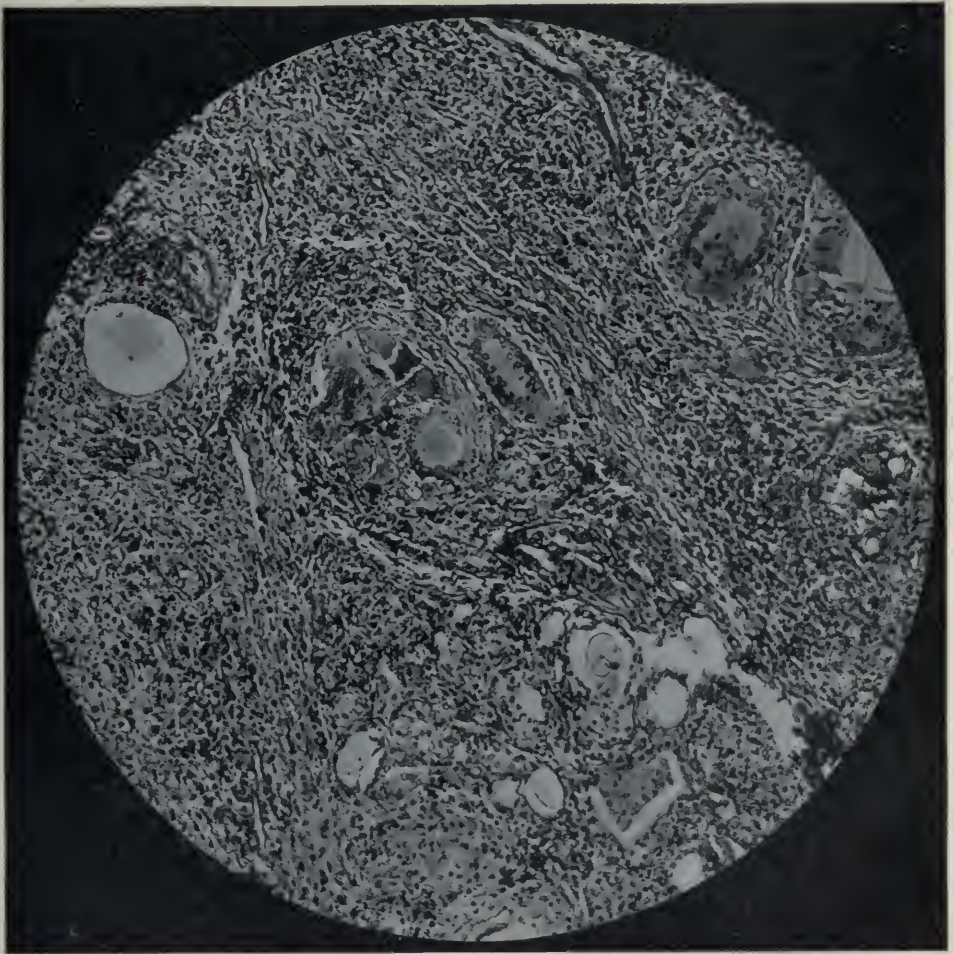


Fig. 2.—Case 3. Thyroid gland showing destruction of follicles and colloid and round cell infiltration and giant cell formation.

April 4, 1919.—A letter from patient bearing this date states that she has in general been well since her last visit; after May, 1916, she continued to take thyroid extract,  $2\frac{1}{2}$  grains daily.

She was married in September, 1916, and went west shortly afterward. During the next six months she gained considerable weight and reached 86 kg., but felt very well and had lots of energy. About a year later she felt dull and stupid, and says that she noticed that her hands and head were getting larger. She doubled the dose of thyroid and promptly became quite

normal again. She has continued on 5 grains daily, most of the time since then and except once when staying at a high altitude, has felt very well. Her weight is now 75 kg. She has had no children (Fig. 2).

**CASE 4.—Myxedema.** (Lab. No. 5. Hospital No. 198640, E. M.) Mrs. R. A housewife, 41 years of age, first entered the hospital Nov. 12, 1914. Her family and past history were unimportant. For two or three years she had been getting sluggish mentally, and had felt chilly and objected seriously to cold weather. Her hair had grown coarse and her skin was dry, and she did not perspire at all. For four or five months she had noticed that her face and hands had become puffy.

**Examination.**—Physical examination showed the characteristic picture of myxedema—puffy face and definite thickening of the subcutaneous tissue. The skin was harsh and dry and the hair coarse and sparse. The thyroid was not enlarged. The blood, urine, blood pressure and Wassermann (blood) were negative. A roentgenogram of the head showed a normal sella turcica. The electrocardiogram showed a normal rhythm and an iso-electric "T" wave.

Nov. 13, 1914.—Basal metabolism was 13 per cent. below normal.

Nov. 14, 1914.—Basal metabolism was 25 per cent. below normal.

Nov. 15, 1914.—Patient started on thyroid extract, 1½ grains per day.

Nov. 17, 1914.—Thyroid extract was increased to 3 grains per day.

Nov. 23, 1914.—No physical sign of myxedema was in evidence. Basal metabolism was 16 per cent. below normal. The electrocardiogram showed a return of the normal "T" wave. Discharged on thyroid extract, 3 grains per day.

Feb. 9, 1915.—Patient called at the hospital to report. She had been perfectly well in feeling and appearance until one month previously, when her thyroid tablets ran out. She had taken none since, and in that time developed some slight dryness of the skin and began to feel cold again. A metabolism determination was not obtained, but she was started again on thyroid extract, this time on 1½ grains per day.

**CASE 5.—Myxedema.** (Lab. No. 63. Hospital No. 807, C. C.) Mrs. G., a housewife, 63 years of age, seen in the consultation clinic for purposes of diagnosis, June 27, 1916. The history was that for eight or nine years she had been troubled by general weakness and by swelling of her ankles and eyelids; also with chilly sensations.

**Examination.**—Physical examination showed a woman with puffy face and hands, and with dry hair and dry, coarse skin. She was rather sluggish mentally. The urine was negative.

June 28, 1916.—A basal metabolism determination was made for differential diagnosis. It was found to be 18 per cent. below normal, and a diagnosis of myxedema was made. Her physician was advised to try thyroid administration.

April 1, 1919.—The patient did not again come under our observation, but on this date her physician wrote that the diagnosis had proved correct. He had found that thyroid extract, 2 grains per day, for a fortnight, alternating with a fortnight without the drug, kept her in perfect health. If she went longer than two weeks without thyroid extract the symptoms would recur.

**CASE 6.—Carcinoma of Thyroid.** (Lab. No. 95. Hospital No. 211392, W. S.) Mr. B., a single man, 56 years of age, a watchmaker, entered the hospital, Oct. 30, 1916, with a history of having noted a swelling in his neck two years before, which had gradually been increasing in size. At about the same time he began to have a coarse tremor of the hands which had been growing worse and had become quite bothersome. Other symptoms referable to abnormal functioning of the thyroid gland were lacking. He had not lost weight.

**Examination.**—Physical examination showed a mass in the neck the size of a large orange, adherent to the trachea and moving with deglutition. It was twice as large on the left side as on the right and apparently involved the entire left lobe and isthmus and a portion of the right lobe of the thyroid.

It was hard and firm and not tender. The skin was somewhat dry and he had a very coarse tremor of the fingers, not at all like the tremor of exophthalmic goiter. He had no tachycardia and no eye signs. Laryngoscopy showed a restriction in motion of the left vocal cord, due probably to pressure on the left recurrent laryngeal nerve.

Oct. 31, 1916.—Basal metabolism was 19 per cent. below normal.

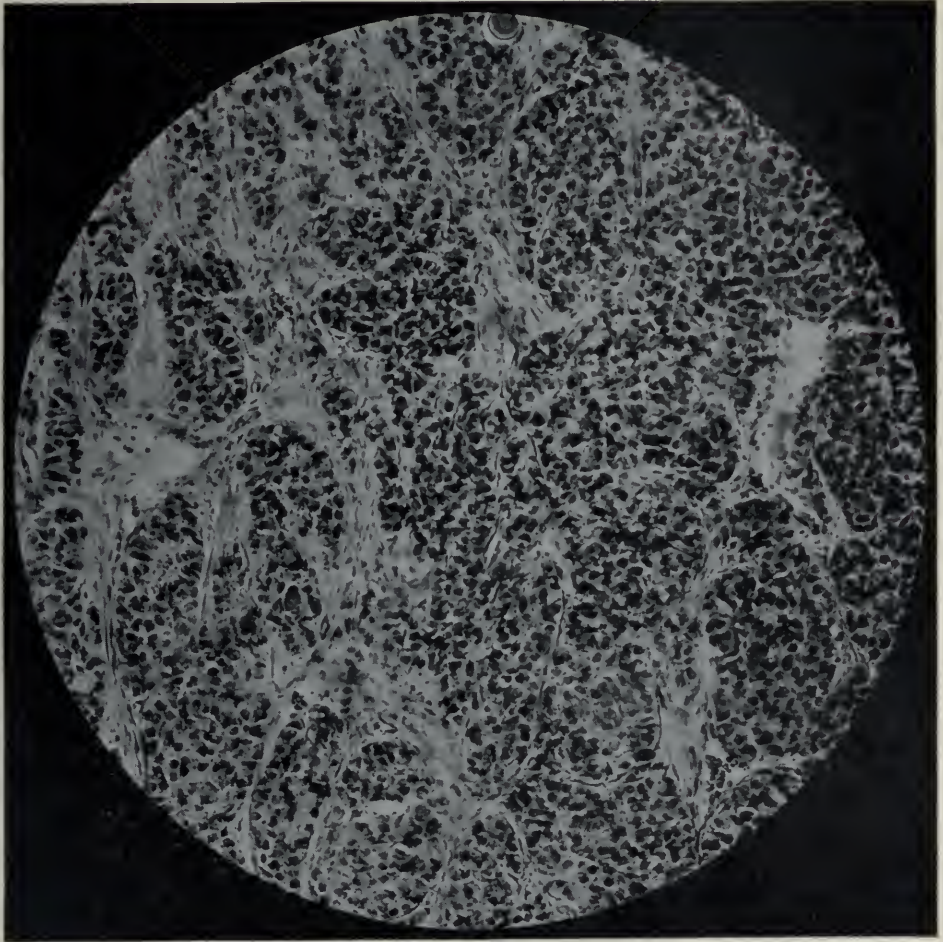


Fig. 3.—Case 6. Carcinoma of thyroid.

*Operation.*—Nov. 4, 1916, the patient was operated on under ether anesthesia, by Dr. G. W. W. Brewster. The tumor was removed and a small amount of normal thyroid tissue was left on the posterior portion of the capsule. The patient made a good ether recovery.

*Pathologic Report.*—A solid tumor, weighing 152 gm. and measuring 9.5 by 8 by 5 cm. It has a smooth red surface. Its section is reddish gray with areas of red and yellow softening and firm white bands. Microscopic examination shows solid columns of cells with small, irregular follicles which contain a dense eosin staining substance, suggesting colloid. The cells show con-

siderable atypicality. The stroma generally consists of narrow strands carrying blood vessels. Occasionally there are wide bands of fibrous tissue. There are numerous widely dilated, thin walled blood spaces. Occasional follicles are to be found lined with normal looking cells and filled with colloid like material. There were occasional mitotic figures. The anatomic diagnosis was carcinoma of the thyroid.

Nov. 13, 1916.—Discharged relieved.

Dec. 21, 1916.—Patient called at the hospital to report. He had been feeling well since his discharge, except for some weakness. The wound was well healed. He had the same coarse tremor; there was some slight evidence of hypothyroidism in that his skin was rather dry and he felt chilly and sweated almost not at all. The basal metabolism was 17 per cent. below normal.

Jan. 23, 1917.—He was seen in the out-patient department. His chief complaint was the tremor of the hands which interfered with his work.

April 15, 1919.—We learned that the patient was still alive but were able to get no information as to his present condition (Fig. 3).

#### DISCUSSION

The existence of a lowered respiratory metabolism in hypothyroidism and the ability of thyroid gland ingestion to raise it, has long been known. The work of Magnus-Levy in this field is by far the most comprehensive. This observer found in a normal woman a rise in the basal metabolism from the normal level to about 15 per cent. above normal after nineteen days thyroid ingestion, beginning with one tablet a day and working up to five tablets per day.<sup>6</sup> In a series of five cretins, three showed a reduction of from 40 to 50 per cent. and two of only 4 and 6 per cent. A case of cachexia strumipriva showed a reduction of 42 per cent.<sup>7</sup> Magnus-Levy used as a standard for comparison normal individuals of like height, weight and sex. This would be satisfactory except for the matter of age. One is at a loss to know with what to compare a cretin's metabolism. Shall we use that of a child of the same height, weight and sex, or shall we use the heat production per unit of surface area of an individual of the same sex and age? The reduction is quite obvious whichever standard is used, but in judging of the proper level to reach and maintain by thyroid administration we are at a loss. As a matter of fact, in the present investigation we have felt that it was probably more reasonable to use the latter criterion, namely, the metabolism per square meter of body surface of normal individuals of the same age and sex. The cretin of mature years, though of the stature of a child, differs from the child in the important respect that it has ceased growing, and hence it seems more reasonable to compare his or her metabolism with that of the adult. Furthermore, in speaking of variations from the normal we are erring on the safe side by using this criterion, for the differences

6. Magnus-Levy, A.: Ueber den respiratorischen Gaswechsel unter dem Einfluss der Thyreoidea, *Berl. klin. Wchnschr.* **32**:650, 1895.

7. Magnus-Levy, A.: Ueber Myxodem, *Ztschr. f. klin. Med.* **52**:201, 1904.

are less marked than they would be if we used the high metabolism of the normal child as a standard of comparison.

Magnus-Levy in his cretins and myxedema patients was able to produce a metabolic rise of anywhere from 17 to 72 per cent. by feeding thyroid preparations. Similarly, DuBois,<sup>8</sup> in his 36-year-old cretin, Benny L., raised the metabolism from about 20 per cent. below normal to normal for men of the same age, by giving thyroid extract, 3 grains per day, for three and one-half days.

More recently Janney<sup>9</sup> has made certain observations on the effect of Kendall's thyroid hormone in various types of thyroid disease. He did not determine the basal gaseous metabolism, but instead followed the nitrogen metabolism and drew his conclusions as to beneficial effects produced by the drug, from the improvement in the nitrogen balance. He found the optimal daily dose of hormone in cases of cretinism, to be 0.75 mg. which corresponds to 4 grains of thyroid tablets, and felt that larger doses are inadvisable.

Our observations of the basal metabolism in hypothyroidism are similar to those found in the literature. Our three myxedema patients before treatment showed variations of 33 per cent., 25 per cent. and 18 per cent. below the normal for their age and sex. Mrs. D. (Case 1), with the most marked grade of myxedema clinically showed the greatest reduction, and Mrs. G. (Case 5), with the mildest, the least. One cretin (Case 2) whose cretinism incidentally must be regarded as of a mild grade, showed a reduction of 23 per cent. below the normal for a woman of her age. The case of cachexia strumipriva (Case 3) is interesting, for after removal of the greater portion of her thyroid her metabolism was 14 per cent. below normal before any clinical manifestations of hypothyroidism were observed. The next observation in her case, while she showed a typical picture of myxedema, was 15 per cent. below normal. Unfortunately, she had been taking thyroid extract for eight days before this second observation was obtained. She reentered the hospital on the surgical service and had received 24 grains of thyroid extract before our attention was called to her case. Presumably her metabolism had been much lower preceding this course of thyroid extract. Similarly, in the case of Mr. B., with carcinoma of the thyroid (Case 6), there was a reduction of 19 per cent. in the metabolism before operation, and of 17 per cent. after operation on both occasions, without definite clinical evidence of hypothyroidism. From the metabolism results, however, it seems reason-

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8. DuBois, E. F.: Metabolism in Exophthalmic Goiter, *Clinical Calorimetry*, XIV, *Arch. Int. Med.* **17**:915 (June) 1916.

9. Janey, N. W.: Studies in Thyroid Therapy, *Arch. Int. Med.* **22**:187 (Feb.) 1918.

able to assume that he was suffering from deficient thyroid secretion, which probably is explained by the fact that before operation his thyroid gland was largely replaced by tumor, and afterward the gland had been removed almost entirely.

As to the effect of thyroid therapy, we agree with Janney that small doses are better than large doses. In the case of Mrs. D. (Case 1) the metabolism was brought to normal and the symptoms of myxedema cleared up by a course of from 6 to  $7\frac{1}{2}$  grains of thyroid extract daily, over a period of about a month. Following this, after continuing with  $1\frac{1}{2}$  grains per day for a year, a course of 3 grains per day for two months raised her metabolism to 11 per cent. above the normal. However, when she was seen two years later, having been taking  $1\frac{1}{2}$  grains daily in the interim, her metabolism was 14 per cent. below normal. It seems likely in this case that the initial dose of thyroid was too large, not only because her metabolism rose above normal, but because between the third and fourth observations, while on  $7\frac{1}{2}$  grains of thyroid extract daily she suffered from considerable nausea and vomiting and general malaise. This was similar to DuBois' experience with the cretin, Benny L., who became nauseated and vomited while taking 3 grains per day. For a maintenance dose with Mrs. D. (Case 1), 3 grains apparently was too large, but  $1\frac{1}{2}$  grains was too small.

In the case of the cretin, Miss L. (Case 2), a total of  $25\frac{1}{2}$  grains of thyroid extract in a week restored the metabolism from 23 per cent. below normal to normal, without untoward results. Then a continuation of  $1\frac{1}{2}$  grains daily for several months served to keep her metabolism from 19 per cent. to 10 per cent. above normal. Following this, after a period of nine months without thyroid, it fell to 11 per cent. below normal. The initial dose of  $4\frac{1}{2}$  grains, therefore, was apparently not too large, but, on the other hand, the maintenance dose of  $1\frac{1}{2}$  grains per day was too large. Altogether, Miss L. was on thyroid therapy for fifteen months, and during that time she increased in height 2.3 cm.

In the case of Mrs. R. (Case 4) 21 grains of thyroid extract in eight days had had no noteworthy effect on the metabolism. Since her discharge from the hospital we have been unable to locate her.

With Mrs. G. (Case 5) we only obtained one observation, that before treatment was begun, but her doctor writes that 2 grains of thyroid extract per day half the time keeps her clinically normal.

It is interesting to contrast these results with those in the case of Miss N. (Case 3) with cachexia strumipriva. With her, initial doses of 3 grains promptly served to restore her metabolism to normal, but from her subsequent history a much larger dose (ultimately 5 grains

daily) has been necessary to keep her in normal health. This is not particularly remarkable, for while the thyroid glands of the cretin and myxedema patients may have had a certain functional activity, Miss N. was practically destitute of thyroid tissue, as only a few very small bits of normal gland were left at operation.

With a view to discovering any relationships which might exist between the metabolism level and the pulse rate, weight and respiratory quotient, we have plotted curves of these factors in the cases of Mrs. D. (Case 1) and Miss L. (Case 2). Between the metabolism level and the respiratory quotient there clearly is no relationship. Between the pulse curve and that of the metabolism level there is in both these patients a rough parallelism, but with definite discrepancies as well, as for example, in the fourth observation on Mrs. D. and the seventh on Miss L., in each of which instances the pulse was lower than in the preceding observation, while the metabolism was higher. Similarly between the weight curves and the metabolism curve there is sometimes a reciprocal relationship, but this is not sufficiently constant but that it might be accidental.

The clinical lessons to be drawn from these studies we believe to be as follows: First, that the level of the basal metabolism is a better index of the degree of thyroid lack than is the clinical picture, and second, that the proper dosage of thyroid preparations can be far more accurately gaged by following the effect on the metabolism than from the appearance and symptoms of the patient. The aim should be to bring the metabolism to the normal level and then find the minimum dose that will keep it there. Janney's method of using the nitrogen balance as a criterion is no doubt good, but it requires a metabolism ward and considerable time and care to make such studies. The basal metabolism on the other hand can be determined quite easily and requires not more than an hour's time. The procedure is especially easy if Benedict's new portable apparatus is used.<sup>10</sup>

We should agree with Janney that large doses of thyroid extract are to be avoided. For the initial treatment 3 grains per day should be sufficient to bring the metabolism to normal, and after the normal level has been reached from 1 to 2 grains may be required to keep it there. The proper maintenance dose will vary among different patients, and should be decided by metabolism determinations.

The importance of following the metabolism in cases of hypothyroidism is emphasized by the fact that our results show that a lowered metabolism, and hence presumably a state of hypothyroidism,

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10. Benedict, F. G.: *Portable Respiration Apparatus for Clinical Use*, Boston M. & S. J. **178**:667 (May 16) 1918.

may occur without clinical manifestations and also by the fact that by thyroid therapy the metabolism can be raised above normal without clinical evidence of thyrotoxicosis.

#### SUMMARY AND CONCLUSIONS.

1. Basal metabolism determinations are reported in three untreated cases of myxedema. All showed a definite reduction below that of normal individuals of the same age and sex.

2. Similarly the basal metabolism in an untreated cretin and in a case of cachexia strumipriva, showed a marked reduction. In the latter case the fall in metabolism antedated the clinical appearance of hypothyroidism.

3. In a case of carcinoma of the thyroid a moderate reduction in basal metabolism was found, both before and after thyroidectomy without clinical evidence of hypothyroidism.

4. The metabolism of all patients studied during thyroid therapy was readily brought to normal, or above, by the administration of thyroid extract.

5. The determination of the basal metabolism forms a sound and convenient method for governing the dosage of thyroid preparations in cases of hypothyroidism, and furnishes a far better guide in this respect than does the clinical picture. It is also of value as a means of differential diagnosis in obscure cases.

6. In the treatment of hypothyroidism doses of from 3 to 4 grains of thyroid extract daily should be ample to bring the metabolism to normal in two or three weeks, and doses of from 1 to 2 grains daily should usually be sufficient to keep it there.

7. Cases of cachexia strumipriva may require larger maintenance doses than those of spontaneous hypothyroidism.

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# THE RELATION OF NEUROCIRCULATORY ASTHENIA TO HYPERTHYROIDISM AS DETERMINED BY THE EFFECTS OF THE INJECTION OF EPINEPHRIN

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Many of the symptoms of neurocirculatory asthenia are so similar to those found in hyperthyroidism, that the theory that this condition is a latent or a very mild thyrotoxicosis has often been advanced. Goetsch has employed epinephrin, given subcutaneously, as a test for latent hyperthyroidism. The detailed technic employed is described by Peabody<sup>1</sup> in a report on the effects of epinephrin on soldiers with irritable heart. I performed the same test in a series of twenty-one consecutive cases in June, 1918,<sup>2</sup> and it is these that I wish to report.

The test, in short, consists of subcutaneous injection of 0.5 c.c. of a 1:1,000 epinephrin solution, with subsequent observations of the pulse rate, blood pressure, tremor, nervousness and throbbing of the blood vessels. Since the systolic blood pressure of these patients is so very labile, they are allowed to rest on a bed until the blood pressure readings have become constant. A rise in pulse rate and blood pressure and an augmentation of the nervous phenomena indicates a positive reaction. A normal individual shows none of these changes. An illustrative protocol may be cited (Table 1).

TABLE 1.—FINDINGS IN ONE CASE FOLLOWING THE INJECTION OF EPINEPHRIN

Time	Pulse	Blood Pressure	Nervousness	Tremor	Cold Hands	Throbbing of Neck Vessels	Remarks
10:12	92	116/65	Slight	Slight	Slight	Slight	
10:18	84	118/65					
10:18*							
10:21	120	144/70	++	++	Slight	+	
10:24	104	144/64	.....	.....	+	+	Vertigo
10:27	88	132/58					
10:32	92	132/62	+++	++	+	+	Respiration 32; deep
10:42	88	136/70	+++	+++	+	+	Patient very restless
10:52	84	130/74	++	++	++		
11:03	88	142/72	++	++	++	+	
11:13	84	132/70	+	+	+	+	
11:23	88	130/75	Slight	Slight	Slight	Slight	Vertigo
11:33	88	136/70	.....	.....	.....	.....	Headache

\* Epinephrin 1:1,000, 0.5 c.c. subcutaneously.

1. Peabody, F. W., et al.: Effects of the Injection of Epinephrin in Soldiers with "Irritable Heart," J. A. M. A. **71**:1912 (Dec. 7) 1918.

2. Boas, Ernst P.: On the Nature of Neurocirculatory Asthenia, Report to Surgeon-General, June 27, 1918.

Various subjective symptoms were complained of by the patients who gave a positive reaction. Chief among these were precordial pain, vertigo, headache, epigastric distress and nausea. Two of the men became very restless, tossing about on the bed with rapid, deep, at times gasping respirations. Four of the patients with negative reactions complained of slight vertigo.

TABLE 2.—SUMMARY OF RESULTS OF TEST IN TWENTY-ONE CASES

Case No.	Thyroid	Family History of Nervousness	Cardiac Symptoms	Gastro-intestinal Symptoms	Bodily Type	Reaction
1	Isthmus palpable	Mother; brother	+	+	Erethic	+
2	Not palpable	Mother; sister	+	+	Erethic	+
3	Not palpable	Mother; brother	+	+	Ptotic	+
4	Not palpable	Mother; two brothers	+	+	Ptotic	+
5	Not palpable	Mother; brother	+	—	?	+
6	Not palpable	Brother	+	—	Stocky	+
7	Isthmus and left lobe	Negative	+	—	Erethic	—
8	Isthmus just palpable	Mother; father	+	—	Erethic	—
9	Isthmus large	Mother; two sisters	+	+	Normal	—
10	Not palpable	Negative	+	Very slight	Erethic	—
11	Not palpable	Mother	+	+	Ptotic	—
12	Not palpable	Mother; sister	+	Slight	Erethic	—
13	Not palpable	Father; mother; three brothers; three sisters	+	+	Ptotic	—
14	Not palpable	Father; sister	+	+	Ptotic	—
15	Not palpable	Mother; sister; brother	+	—	Ptotic	—
16	Not palpable	Negative	+	—	Stocky	—
17	Not palpable	Brother	+	—	Ptotic	—
18	Not palpable	Mother	+	—	Normal	—
19	Not palpable	Father	+	—	Ptotic	—
20	Not palpable	Mother	+	?	Normal	—
21	Not palpable	Negative	+	—	Normal	—

It is noteworthy that only four of the patients had palpable thyroids and that only one of these gave a positive reaction. None of the men had exophthalmos, nor any other eye signs that are seen in exophthalmic goiter. The bodily type of the individual seemed to have no influence on the result of the test. By the erethic type are meant men of good build, with high color, who have marked vasomotor instability, manifested by frequent flushing, vertigo on change of posture, and headaches. By the ptotic type are meant men who conform to what is often known as the tubercular habitus. All but four of the men give a family history of "nervousness." Nervousness as used by these patients in describing the symptoms of their relatives usually means a nervous instability similar to that which they exhibit.<sup>3</sup> Four out of six of the positive cases have gastro-intestinal symptoms of a func-

3. Robey, W. H., Jr., and Boas, E. P.: Neurocirculatory Asthenia, *J. A. M. A.* **71**:525 (Aug. 17) 1918. Oppenheimer, B. S., and Rothschild, M. A.: The Psychoneurotic Factor in the Irritable Heart of Soldiers, *J. A. M. A.* **70**:1919 (June 22) 1918.

tional nature; while only six out of fifteen of the negative cases show this association. However, the series is too small to attach any significance to this fact. Thus an analysis of the epinephrin reaction in this group of cases shows that it is impossible to predict from any of the criteria that we have at present, whether or not any particular case of neurocirculatory asthenia is sensitive to epinephrin or not.

In a series of sixty-five cases, Peabody found positive reactions in 60 per cent. of the cases. In my smaller series only 28.6 per cent. of the men reacted positively. Granted that the test gives an indication of latent hyperthyroidism, it is clear that all cases of neurocirculatory asthenia are not to be explained on this basis. Even in the positive cases the thyroid hyperfunctioning may be only a symptom and not a cause of the condition. Addis and Kerr,<sup>4</sup> in a study of the frequency with which the symptoms of neurocirculatory asthenia occur in recruits with and without thyroid enlargement, found that there was no relation between thyroid enlargement and the occurrence of the syndrome. Lewis<sup>5</sup> found palpable enlargement of the thyroid in only 4 per cent. of his cases of irritable heart. Furthermore, as has been pointed out before,<sup>3, 6</sup> the typical eye signs of exophthalmic goiter are rarely, if ever, found in patients with neurocirculatory asthenia. The tremor in the latter disease is much coarser, and finally, in spite of the fact that the symptoms may exist for years, cardiac hypertrophy, such as is found in goiter, is never seen in these men with "irritable heart." Undoubtedly, different causes contribute to the appearance of the symptom-complex. Further study, particularly with a view to grouping the cases according to whether the symptoms are chiefly cardiovascular, gastro-intestinal, or mental is essential to shed further light on the true nature of this common but baffling condition.

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4. Addis, T., and Kerr, W. J.: Relative Frequency in Recruits With and Without Thyroid Enlargement of Certain Signs and Symptoms Which Occur in Neurocirculatory Asthenia, *Arch. Int. Med.* **23**:316 (March) 1919.

5. Lewis, T.: Reports on Soldiers Returned as Cases of "Disordered Action of the Heart," Medical Research Committee, Special Report Series, No. 8, London, 1917.

6. Cohn, A. E.: The Effort Syndrome, *J. A. M. A.* **71**:3132 (Dec. 25) 1918.

## THE SIGNIFICANCE OF ABNORMALITIES IN THE FORM OF THE ELECTROCARDIOGRAM \*

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Much interest has recently been shown in the relation of changes in the form of the electrocardiogram to disturbances of the myocardium. This interest is centered for the most part about changes in the form of the ventricular portion of the electrocardiogram, which have been interpreted as indicative of faulty conduction of the cardiac impulse through the ventricles. The abnormal form of the electrocardiogram, to which attention is directed in this paper, consists in a prolongation of the initial group of waves of the ventricular portion, the so-called Q-R-S group, with notching or splitting of the main wave, the R wave. A consideration of this portion of the electrocardiogram is important, as it renders valuable information concerning the state of the myocardium, and has proved of distinct value in determining the diagnosis and prognosis in numerous cases of heart disease.

It is a well established fact that the electrical phenomenon accompanying cardiac activity, which is expressed by the electrocardiogram, begins before the actual contraction of the heart muscle, and the first series of waves constituting the ventricular portion of the electrocardiogram represents, in part, the spread of the cardiac impulse into and through the ventricles. A disturbance in the passage of cardiac impulse along the intraventricular conducting system and through the ventricular musculature causes a change in the form of the first portion of the ventricular curve. The prolongation of the Q-R-S group indicates that the time required for the complete activation of the ventricles is lengthened, and the notching probably indicates that the activation of the various portions of the ventricles is not taking place in its proper sequence. This interpretation of the type of abnormal electrocardiogram which has been mentioned is generally accepted. The purpose of this paper is to present some facts which apparently throw light on the mechanism by which the conduction into and through the ventricles is sometimes disturbed, and an interpretation of the abnormal electrocardiogram is offered which differs from that which has been generally expressed.

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In a paper which I published in 1916,<sup>1</sup> electrocardiograms were reproduced which demonstrated that the type of abnormal electrocardiogram which is here under discussion may result when the stimulus of the heart beat reaches the ventricles before they have fully recovered from previous activity and when they are in a state which may be conveniently termed functional fatigue. It was pointed out in this paper that under these circumstances the disturbance of the intravenous conduction is dependent on the fact that an insufficient time has elapsed for the recovery of the ventricles and the curves reproduced show that when a sufficient length of time has elapsed the following electrocardiogram has a form which is much nearer that yielded by the normal heart. This is especially well seen in a record from a case of sino-auricular block in which an idioventricular contraction usually occurs during the latter part of the pause caused by the block. This idioventricular contraction precedes by a short interval the auricular beat, which sends down a stimulus to the ventricles, stimulating them soon after the completion of the idioventricular contraction. The interval of time elapsing between the idioventricular contraction and the stimulation of the ventricles by the impulse sent down by the auricular contraction varies, and the form of the ventricular complex produced by the second ventricular activity also varies in form. A study of a large series of records from this case shows that the form of the complex yielded by the second ventricular contraction bears a direct relationship to the period of rest that precedes it. When the period of rest is very short the ventricles fail to respond to the impulse descending from the auricles. When the period of rest is somewhat longer, the ventricles respond, but yield a complex with a much prolonged Q-R-S group and with well defined notching of the R wave. When the period of rest is still further prolonged the ventricular complex approaches the normal complex in form. This is shown in Figure 1 of the previous paper.

The records of this case demonstrate, therefore, that so-called functional fatigue may be responsible for the abnormal form of the ventricular complex under discussion, and in this instance an anatomic lesion can hardly be considered as playing a rôle in its production.

In the paper that has been mentioned records of a case of auricular fibrillation were reproduced in which the same abnormalities of form are seen in the ventricular portion of the electrocardiogram whenever the diastolic pause preceding the ventricular contraction is relatively short, while following longer pauses the ventricular complex assumes

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1. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *Arch. Int. Med.* **18**:830 (Dec.) 1916.

a form much nearer the normal. The interpretation seems justified that the disturbance in conduction through the ventricles in this case is dependent on lack of time for recovery, and that when sufficient time elapses between beats, intraventricular conduction apparently takes place at a relatively normal rate and in a relatively normal manner. (Figs. 4 and 5 of the previous paper.)

The evidence of these two cases and others reported with them has led to the belief that in cases in which the ventricular complexes constantly show certain abnormal forms there may be functional changes in the heart which prevent the normal recovery of intraventricular conduction during diastole. This explanation for the cause of the abnormalities of the electrocardiogram under discussion has not, however, been emphasized by those who have since published papers on this subject. Thus Oppenheimer and Rothschild<sup>2</sup> have attempted to correlate gross and histologic changes in the hearts of several patients with the abnormal form of electrocardiogram without considering the possibility that physiologic rather than anatomic changes might be responsible for the altered form of the electrocardiograms. Although they mention the cases showing temporary changes in the electrocardiograms, they seem to consider that they belong to another type of case from those which they describe. This division of the cases does not seem to me to be justified.

Following this paper by Oppenheimer and Rothschild there seems to have been a general acceptance in this country of the idea, either stated or implied, that abnormal forms of electrocardiograms are indicative of intraventricular block caused by localized subendocardial lesions. This is to be noted in the papers of Blackford, Willius and Haines,<sup>3</sup> Neuhof,<sup>4</sup> Carter<sup>5</sup> and Willius.<sup>6</sup> Wedd,<sup>7</sup> whose paper deals with less pronounced changes in the form of the electrocardiogram, recognizes, however, the possibility of functional derangement of intraventricular conduction without localized lesions in the conducting system. Willius goes so far as to state that "arborization block or impaired intraventricular conduction is dependent on graphic records

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2. Oppenheimer, B. S., and Rothschild, M. A.: *Electrocardiographic Changes Associated with Myocardial Involvement*, J. A. M. A. **69**:429 (Aug. 11) 1917.

3. Blackford, J. M., Willius, F. A., and Haines, L. B.: *Operative Risk in Cardiac Disease*, J. A. M. A. **69**:2011 (Dec. 15) 1917.

4. Neuhof, S.: *The Clinical Significance of the Abnormally Wide Ventricular Deviation in the Electrocardiogram*, Arch. Int. Med. **22**:45 (July) 1918.

5. Carter, E. P.: *Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrio-Ventricular Bundle Branches and Their Terminal Arborization*, Arch. Int. Med. **22**:331 (Sept.) 1918.

6. Willius, F. A.: *Arborization Block*, Arch. Int. Med. **23**:431 (April) 1919.

7. Wedd, A. M.: *The Clinical Significance of Slight Notching of the R Wave of the Electrocardiogram*, Arch. Int. Med. **23**:515 (April) 1919.

for its recognition. It is now generally accepted to indicate disease of the subendocardial myocardium and evidence of serious functional cardiac disturbance. The involvement occurs in the subendocardial or Perkinje plexus." This statement is made in spite of the fact that the postmortem examination of five hearts revealed no definite localizing lesions, but rather diffuse degenerative processes involving the myocardium.

Carter has reported a case yielding abnormal electrocardiograms in which a very careful histologic study of the subendocardial structures was made. He considers that there existed a causal relation between the abnormal electrocardiograms and the sclerosis that we found in the atrioventricular bundle branches and their terminal arborizations. In this case the explanation of the abnormal electrocardiograms seems well grounded, although not definitely proved. There was found a discrepancy between the amount and position of the sclerotic changes in the ventricular conducting system and the anticipated form of the electrocardiogram, suggesting that some other factor than the anatomic lesion may have been operative.

Fridericia and Møller<sup>8</sup> also report a case showing abnormal electrocardiograms in which there was an extensive lesion in the intraventricular system causing, the authors consider, intraventricular block.

I have recently had an opportunity of studying a case which seems to throw some new light on the causation of the abnormal form of electrocardiograms, which I wish to report before considering the underlying causes of the disturbance of intraventricular conduction.

#### CASE REPORT

A man, 63 years of age, a telegraph operator, entered the hospital with severe symptoms of cardiac decompensation, showing marked dyspnea, edema of the extremities and cyanosis. His history revealed no definite etiology, but there was an unsubstantiated history of syphilis. He had had cardiac symptoms, especially palpitation, for about a year, and had dyspnea for six months, with frequent attacks of nocturnal dyspnea. From the examination a diagnosis of arterial sclerosis, chronic myocarditis, auricular fibrillation and mitral insufficiency were made. Electrocardiograms obtained May 10, 1917, showed the ventricular rate to be 135 per minute, and the form of the ventricular portion was abnormal in all leads, the initial group of waves being prolonged to 0.170 to 0.180 second (maximum normal = 0.100 sec.) and definite notching was present. The form of the electrocardiogram suggested right branch bundle block, but was not typical, and indicated a high degree of derangement in the intraventricular conducting system (Fig. 1).

This patient was given a single dose of a standardized tincture of digitalis, 6 c.c., the dose being smaller than that usually administered in cases of auricular fibrillation in this clinic, because of a history of having taken the drug in small doses up to the time of admission to the hospital. The patient responded

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8. Fridericia and Møller, P.: Et Tilfælde af Myocarditis, lokaliseret til septum Ventriculorum, med ejendommelise abnormiteter; Elaktrokaardiogrammet, *Hospitalstid.* **60**:573 (June 13) 1917; **60**:597 (June 20) 1917.

remarkably well to the drug and electrocardiograms obtained two days later showed a ventricular rate of 69 per minute. The form of the ventricular complexes was strikingly changed. The initial group of waves had a duration of from 0.92 to 0.10 second, and the notching of the main wave had almost entirely disappeared (Fig. 2). The clinical improvement was also striking. No more digitalis was administered at this time and the ventricular rate gradually increased. Electrocardiograms obtained May 13 and May 15, showed a rate of 85 per minute, with increased arrhythmia (Fig. 3). In the records the ventricular complexes have distinctly more notching and prolongation of the initial group of waves than that obtained when the ventricular rate was 69 per minute. A feature of these records is the definite abnormality of form seen in the complexes yielded by the ventricular contractions which are preceded by short diastolic periods. Under these conditions the complexes have a form approaching that seen when the heart was beating at a rate of 135 per minute.

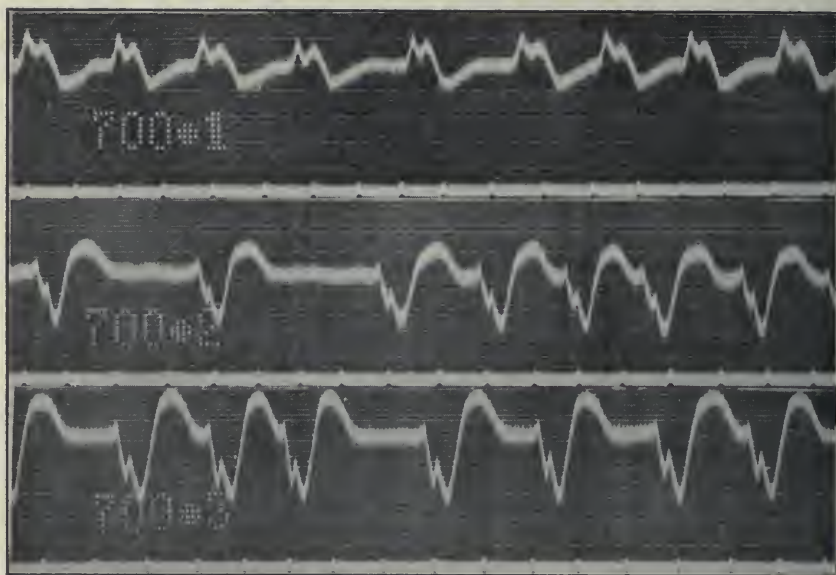


Fig. 1.—Electrocardiogram, three usual leads, obtained May 10, 1917, when patient first entered the hospital. Ventricular rate, 135 per minute. Initial group of waves of ventricular complex from 0.170 to 0.180 second in duration.

The administration of digitalis again slowed the heart and caused a disappearance of the electrocardiographic evidence of disturbance of intraventricular conduction. Cardiac efficiency became much improved and the patient left the hospital with instructions to use the tincture of digitalis constantly. These instructions were not carried out, however, and the patient returned six weeks later with slight signs of cardiac inefficiency and with a ventricular rate of from 144 to 158 beats per minute. At this time, however, the electrocardiograms failed to reveal any prolongation of the initial waves of the ventricular complexes, and only slight notching was present (Fig. 4). In other words, at this time, in spite of a higher ventricular rate than that first seen, there was practically no evidence of a disturbance of intraventricular conduction. The use of the tincture of digitalis again slowed the heart, and a record obtained one month after the second admission showed a ventricular rate of 61 beats per minute, with practically no change in the form of the electrocardiograms.

It is difficult to conceive how the disturbance in the intraventricular conduction which was evidently present in this case when first observed could have been caused by an anatomical lesion involving the subendocardial tissues and the arborization of the ventricular conductory system, because of its rapid disappearance when the heart rate became slowed by digitalis. The fact that the disturbance of intraventricular conduction, the so-called arborization block, did not return later with the increase in ventricular rate also indicates that some improvement in the physiologic processes of the heart had occurred during the period of treatment.

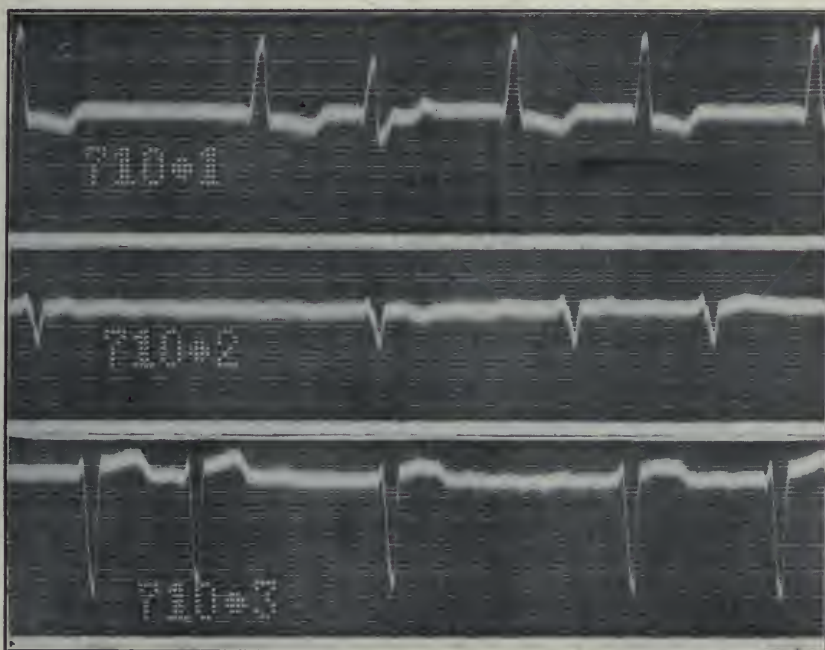


Fig. 2.—Electrocardiogram obtained May 12, 1917, after a single dose of digitalis had been given. Ventricular rate 69 per minute. Striking change in form of complexes. Initial group of waves of ventricular complex from 0.092 to 0.100 second in duration.

A consideration of this case as well as of those that have already been reported and reviewed brings out the necessity for another explanation than that which had been offered by Oppenheimer and Rothschild and others to account for the abnormalities in the form of the electrocardiograms seen in these cases.

The term functional fatigue has already been used to account for the derangement of intraventricular conduction. Of course, a recognized change in structure may bear a causative relation to a derange-

ment in a physiologic process, but in the light of the cases that I have reported this association can by no means be taken for granted, and other so-called physiologic factors must come into play in these cases.

I wish to discuss briefly the possible physiologic factors that seem to me likely to play a rôle in the production of disturbances in intraventricular conduction, and which in turn may be worthy of consideration as a factor in the production of cardiac inefficiency in cases of heart disease.

In the cases under consideration an improvement in the state of the intraventricular conduction takes place during the diastolic periods when the heart is at rest. But instances are seen when the diastolic period is not long enough to allow complete recovery, and in the case reported in this paper the recovery of intraventricular conduction is slower at

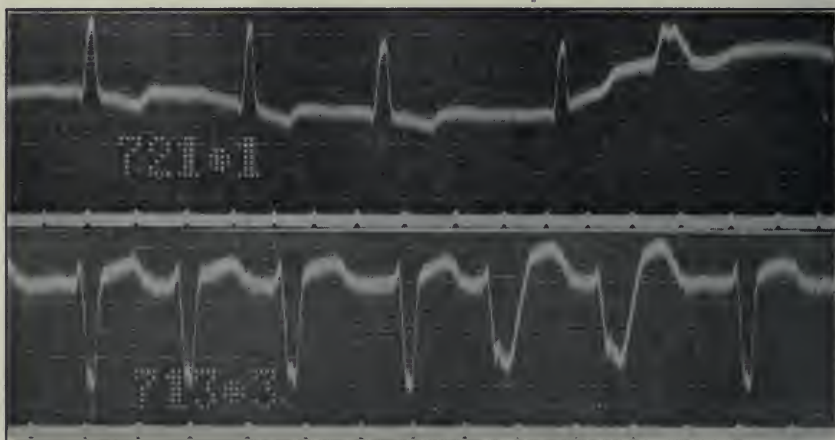


Fig. 3.—Electrocardiograms obtained May 13 and May 15, 1917. Ventricular rate, 85 per minute. The form of the ventricular complexes and the duration of the initial group of waves depend on the length of the preceding diastole. First and third leads are shown.

one time than at another. It may be inferred from these observations that certain metabolic processes occur during ventricular activity which affect the function of the conducting mechanism, and that a definite time is required for the recovery of the ventricles before the conducting of the cardiac impulse proceeds through them in a normal manner. The length of time required for this recovery may be increased distinctly in damaged hearts, and under certain conditions the diastolic rest may be continually insufficient to allow complete recovery of the intraventricular conducting system. This is apparently the cause of the abnormal electrocardiograms shown in Figure 1. Figure 3 shows, however, that the degree of recovery of the conducting system is

dependent on the length of the cardiac rest afforded by the diastolic period.

I wish to suggest that the derangement of intraventricular conduction which is indicated by the abnormal form of the electrocardiogram may be caused in these cases by the presence of acid metabolites, and that these acid metabolites are present in increased amounts when there is a deficient supply of oxygen to the tissues involved.

The basis for this explanation is the work of Fletcher and Hopkins<sup>9</sup> on the effect of diminished oxygen supply on muscle activity and the work of Mines<sup>10</sup> and of Burridge<sup>11</sup> on the effects of changes in hydrogen ion concentration on conduction through the ventricles.

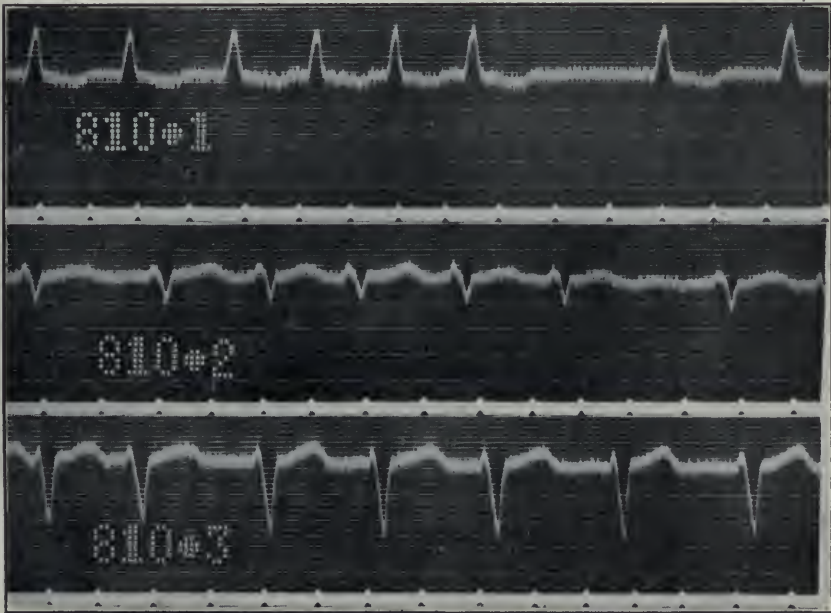


Fig. 4.—Electrocardiogram obtained June 29, 1917. The ventricular rate is 158 per minute, but the abnormalities of the ventricular complexes previously seen do not occur.

Fletcher and Hopkins have carried out an investigation on lactic acid in amphibian muscle, and state that there is a large body of well-known evidence which indicates that the disposal of acid products—whatever the site of it may be—is most efficient when conditions for

9. Fletcher and Hopkins: Lactic Acid in Amphibian Muscle, *J. Physiol.* **35**:247, 1907.

10. Mines: On Dynamic Equilibrium in the Heart, *J. Physiol.* **46**:349, 1913.

11. Burridge: Propagation of Contraction in the Frog's Heart, *J. Physiol.* **45**:6, 1912.

oxidative processes are most favorable, and that it is incomplete when these conditions are unfavorable. Their experiments show that the lactic acid formed in muscle follows this rule, and its disappearance from muscle is dependent on the oxygen supply.

With these facts in mind, it is not difficult to conceive that acid metabolites tend to accumulate in the heart muscle when the oxygen supply is insufficient to meet the demands of the rapidly beating heart. In a number of the hearts showing delayed intraventricular conduction marked sclerosis of the coronary arteries have been observed, notably in the series of Oppenheimer and Rothschild<sup>2</sup> in which twelve of the fourteen hearts examined postmortem showed well defined coronary artery sclerosis. This lesion may, therefore, be considered responsible for an inadequate oxygen supply to the heart muscle, which results in an excessive production of acid metabolites.

Burridge<sup>11</sup> has shown that the addition of acid to the fluid with which the frog's heart was perfused caused a delay in the conduction of the impulse. He states further that if sufficient acid were added to cause the heart to stop beating, sodium bicarbonate neutralization brought back the beat, but with markedly delayed conduction of the impulse through the ventricle. Mines<sup>10</sup> has used these experiments to account for certain changes in the electrocardiogram which result from increased frequency of the heart beat which he believes may lead to changes in the hydrogen ion concentration in some region of the muscle. If these experiments can be considered as holding good for the chemical changes that occur during the cardiac action of the human heart, they seem to justify the hypothesis that any change which diminishes the oxygen supply to the heart muscle will favor the accumulation of acid metabolites and consequently cause a derangement in the propagation of the cardiac impulse through the ventricles. This derangement would become apparent whenever the diastolic rest is of insufficient duration to allow the removal of the acid metabolites from the ventricular structures. Sclerosis of the coronary arteries would furnish the condition for the increased production of acid metabolites and also tend to delay their removal. Myocardial lesions, such as a fibrosis, would perhaps also tend to produce these effects by lessening the efficiency of the blood supply to the ventricular structures.

It should be stated that an objection to the foregoing hypothesis may be raised in that there is no evidence that acid metabolites are produced by the activity of the conducting system. Erlanger<sup>12</sup> was unable to discover the production of acid in the conducting system as a result of its activity. The effect of acid produced in the muscle on conduction is therefore open to question.

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12. Erlanger, J.: Personal communication.

## SUMMARY

Certain abnormalities in the form of the electrocardiogram are recognized as evidence of faulty conduction of the cardiac impulse through the ventricles. These abnormalities consist of a prolongation of the time required to complete the first series of waves, the Q-R-S group of the ventricular part of the electrocardiogram and notching of the main wave of the group. An attempt has been made by several writers to associate faulty conduction of the cardiac impulse within the ventricles with anatomical lesions involving the intraventricular conducting system. This association may be correctly assumed in some cases, but in this paper cases are reported which seem to prove that faulty conduction through the ventricles may depend on what has been termed "functional fatigue." Examples are cited in which derangement of ventricular conduction has resulted from lack of time for conduction recovery after a ventricular contraction. In the case reported, distinct improvement in ventricular conduction followed slowing of the heart rate, when longer diastolic pauses were present. The rate of recovery of conduction was observed also in this case to become more rapid with improved circulatory efficiency.

The hypothesis is advanced that in the cases referred to in this paper the disturbance of intraventricular conduction is the result of the presence of acid metabolites in the ventricular structures, and that sclerosis of the coronary arteries and perhaps other lesions causing an insufficient blood supply to the ventricles are responsible for the presence of the acid metabolites, as it has been shown that these accumulate whenever the oxygen supply to muscle is inadequate. This hypothesis renders an anatomic lesion in the subendocardial structures unnecessary to account for the disturbance of the intraventricular conduction, although the effect of acid produced in the muscle on conduction is still open to question.

## THE USE OF LABORATORY METHODS IN THE DIAGNOSIS OF EARLY HYPERTHYROIDISM

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PHILADELPHIA

The following study was prompted by the desire to discover means of differentiating early or borderline hyperthyroidism from functional cardiac disorder through the aid of the laboratory.

The recognized laboratory test for hyperthyroidism is that for basal metabolism as developed by Rubner, Magnus-Levy, Salomon, DuBois, Henderson, Peabody and others. The respiratory gas interchange as estimated by this test, shows an increase of from 50 to 80 per cent. of oxygen consumed in several cases, and from 20 to 50 per cent. increase in mild to moderately severe cases of hyperfunctional activity of the thyroid.

Such an apparatus was not available for the present study. There are still but few in use in this country. Either the Benedict or a modified Haldane is the apparatus of choice. Both require quite a measure of special skill in their manipulation.

Other more simple laboratory tests were applied: The sugar tolerance test;<sup>1</sup> the epinephrin test;<sup>2</sup> tests for nitrogen loss; tests for acidosis.<sup>3</sup> These tests can readily be learned by every clinician interested, and may be performed in a small office laboratory, either by the physician himself or his assistant. The epinephrin test is carried out at the bedside or in the physician's office.

The work recorded in this paper was completed at the Base Hospital, Camp Dix, N. J. As regards the study of nitrogen elimination, I would have wished that facilities and assistance had permitted more exact metabolic studies, especially in weighing diets, and estimating nitrogen intake. Later studies will better satisfy research requirements. For most exact estimations for acidosis, Van Slyke's plasma CO<sub>2</sub> test<sup>3</sup> gives the most reliable and direct results. The tests reported here: for total acidity of urine, sodium bicarbonate tolerance and urinary ammonia are also reliable as an indirect measure of blood alkali reserve. The group of patients studied were admitted to the

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1. Janney, N. W., and Isaacson, V. I.: A Blood Sugar Test, J. A. M. A. **70**:1131 (April 20) 1918.

2. Goetsch, Emil: Newer Methods in the Diagnosis of Thyroid Disorders: Pathologic and Clinical, New York State J. M. **18**:259 (July) 1918.

3. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis, J. Biol. Chem. **30**:289 (June) 1917.

cardiovascular service for observation, diagnosis and treatment, later to be discharged or transferred. Seven patients, from clinical symptoms, undoubtedly had exophthalmic goiter. About twenty other patients were studied at the same time with the goiter patients. Some of the twenty, by symptoms alone, could most readily be said to have a functional cardiac disorder. Both groups were studied by means

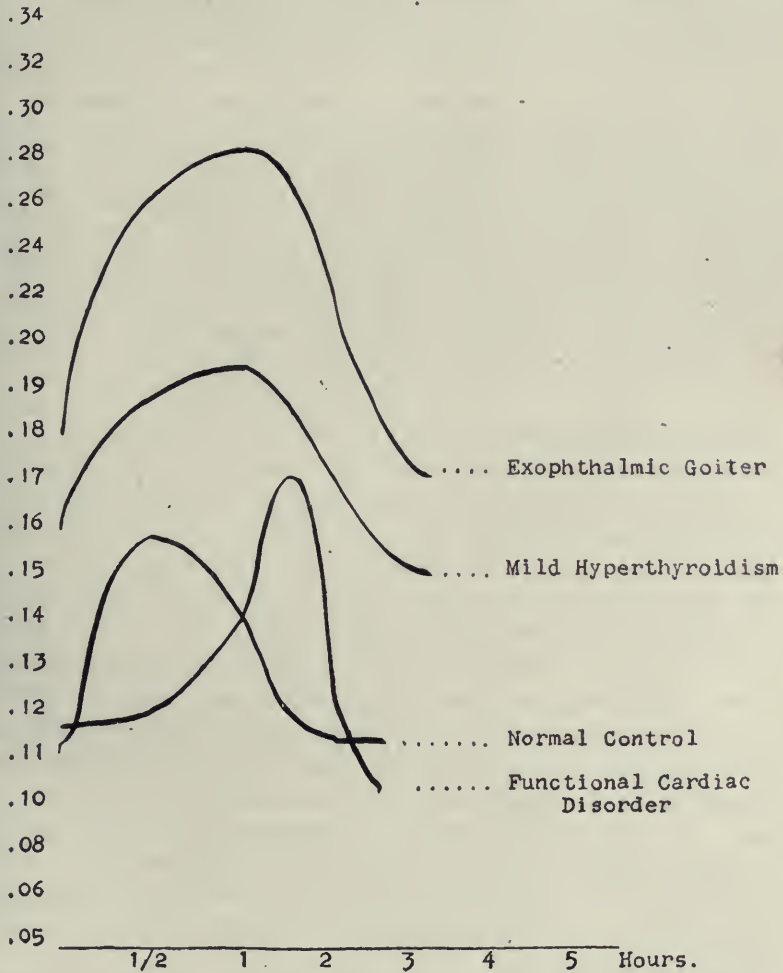


Fig. 1.—Blood sugar assimilation curves for the three groups studied, compared with the normal curve.

of the laboratory methods mentioned above. When results were compared, four or five from the larger group are called in this paper early or mild hyperthyroidism.

The cases diagnosed by laboratory study as hyperthyroidism, presented symptoms suggesting a derangement of the sympathetic nervous

system, namely: tremors, sweating, nausea, insomnia, nervousness and headaches. The characteristic symptoms of the patients remaining in the functional cardiac disorder group directed attention to the heart and circulatory system, namely: precordial pain (especially), dyspnea on exertion, tachycardia, syncope, cyanosis and exhaustion.

It was found that a palpable and even a moderately enlarged thyroid may be present in both groups. The laboratory tests seemed to provide a means of separating the hyperactive thyroid from the simple hypertrophied gland found associated with functional cardiac disorder.

I am aware of the intimate correlation and interaction of the internal secretory glands and that metabolic and functional derangements pointing to a dysfunction of one endocrine system does not preclude hormone disorders of other glands. Nevertheless, any effort to differentiate true hyperthyroidism from true cardiac neurosis, is of value not only from a therapeutic standpoint, but equally from a preventive one—to institute prophylactic treatment before exophthalmus, thyroid and myocardial injuries become permanent.

#### I. RESULTS OF THE BLOOD SUGAR TOLERANCE TEST

The results are to be studied in relation to normal blood sugar tolerance figures. The average blood sugar fasting level is represented by 0.095 per cent. glucose concentration. Normal figures range between 0.07 and 0.12 per cent. concentration; 0.18 per cent. concentration is the average threshold level for blood sugar, above which point sugar often overflows into the urine in amounts large enough to be detected by the ordinary qualitative sugar tests. In but few of the cases here recorded could definite positive tests for glycosuria be reported. Duplicate tests were often made in the blood sugar estimations, and the average recorded; especially was this done in estimating the fasting level, prior to sugar ingestion. In the tolerance tests here recorded, when the blood sugar curve, following the ingestion of a 40 per cent. solution of glucose or of sucrose, 1.75 gm. per kilogram of weight, extends over two or two and one-half hours before returning to or below the initial fasting level, the assimilation for glucose is said to be delayed. When glycosuria results, the tolerance for sugar is said to be decreased.

Table 1 gives the results of the sugar tolerance test in seven cases of exophthalmic goiter. With two exceptions, the blood fasting level was high, that is, hyperglycemia was present in five of the seven patients. The assimilation curves were prolonged, with one exception, over two and one-half hours, and the peaks of the curves were characteristically high. Two of the five cases in which the urine was examined, at hourly intervals, following the sugar ingestion, showed decreased tolerance or glycosuria.

TABLE 1.—BLOOD SUGAR TESTS IN EXOPHTHALMIC GOITER

Case	Fasting Level, per Cent.	After Sugar Ingestion							
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.
H. T. ....	0.085	0.176	0.184	0.172	0.160	0.150	0.174	0.160	0.140
R. H. ....	0.154	0.150	0.182	0.184	0.180	0.162	.....	0.146	.....
B. C. ....	0.146	0.190	.....	.....	0.176	0.145	.....	.....	.....
R. B. ....	0.095	0.100	0.222	0.168	0.156	0.152	0.146	.....	0.140
B. E. ....	0.127	0.134	0.162	0.200	0.164	0.166	0.145	0.135	0.135
W. J. ....	0.142	0.230	0.188	0.174	0.188	0.142	0.142	.....	.....
D. G. ....	0.180	0.262	0.282	0.230	0.216	0.193	0.170	0.170	.....

TABLE 2.—BLOOD SUGAR TESTS IN EARLY HYPERTHYROIDISM

Case	Fasting Level, per Cent.	After Sugar Ingestion							
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.
L. C. ....	0.142	0.160	0.168	0.190	.....	0.160	0.160	0.138	0.122
L. C. ....	0.160	.....	0.195	.....	0.180	0.155	0.150	.....	.....
A. L. ....	0.130	0.200	.....	0.184	0.153	0.150	0.140	0.131	.....
B. A. ....	0.115	.....	0.206	0.200	0.152	0.140	0.130	0.120	.....
R. J. ....	0.105	.....	0.192	.....	0.158	.....	0.116	0.110	.....
G. S. ....	0.137	0.190	0.230	0.202	0.215	0.202	.....	0.147	.....
V. G. ....	0.110	0.240	0.186	0.185	0.150	0.130	0.120	0.110	.....
M. G. ....	0.127	0.176	0.160	.....	0.280	0.200	0.146	.....	.....

TABLE 3.—BLOOD SUGAR TESTS IN FUNCTIONAL CARDIAC DISORDERS

Case	Fasting Level, per Cent.	After Sugar Ingestion							
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.
S. D. ....	0.140	0.200	0.130	0.140	0.132	0.140	.....	.....	.....
S. F. ....	0.144	0.192	0.180	0.170	0.170	0.162	0.148	0.142	.....
T. V. ....	0.140	0.180	.....	0.156	0.148	0.115	0.130	.....	.....
B. F. ....	0.130	0.170	0.190	0.165	0.142	0.132	0.130	.....	.....
J. J. ....	0.100	.....	0.164	.....	0.160	0.140	0.130	0.120	.....
L. E. ....	0.119	0.119	0.140	0.173	0.125	0.102	0.110	.....	.....
S. C. ....	0.095	0.125	0.081	0.093	0.100	0.100	.....	.....	.....
N. H. ....	0.110	.....	0.130	0.119	0.110	0.100	.....	.....	.....
R. R. ....	0.083	0.074	0.070	0.092	0.074	0.090	.....	.....	.....
E. W. ....	0.105	0.190	0.166	0.130	0.090	0.095	.....	.....	.....

The fairly high fasting level, or hyperglycemia; the high peak and the delayed assimilation curve in each of the nine cases classified as mild hyperthyroidism (Table 2), shows the similarity which exists, from a laboratory standpoint, between this group and the exophthalmic goiter patients. Two of the six patients whose urine was examined during the test showed glycosuria or decreased tolerance.

The group reviewed in Table 3 represents those patients classified clinically as functional cardiac disorder. Two of the ten patients showed a delayed assimilation of sugar; however, the remaining tests performed on the entire group gave normal figures. The fasting blood sugar level was slightly higher than normal in four of the patients, though the same fasting level was found in normal controls. The long walk from the ward to the laboratory just prior to the blood withdrawal may have been a factor. The normal controls were laboratory technicians actively engaged at work, the hour preceding the test. Note, therefore, the much lower fasting level, the lower peak, and the more rapid assimilation in this cardiac group compared with the previous tables. The sugar tolerance was not decreased in any of the five patients examined for glycosuria.

TABLE 4.—BLOOD SUGAR TESTS IN MISCELLANEOUS DISORDERS

Case	Diagnosis	Fasting Level, per Cent.	After Sugar Ingestion								Glycosuria, Hourly Tests
			½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.	
F. J.	Hypopituitarism	0.080	.....	0.188	0.180	.....	0.120	.....	0.115	0.096	None
M. A.	Simple goiter	0.100	.....	0.118	0.200	0.188	.....	0.102	.....	.....	None
L. L.	Simple goiter	0.100	0.085	0.200	0.100	0.100	.....	.....	.....	.....	None
P. B.	Hysteria	0.105	0.108	0.107	0.121	0.094	0.089	.....	.....	.....	.....
K. N.	Moron	0.105	0.180	0.120	0.118	0.111	0.098	0.092	.....	.....	.....
C. F.	Endarteritis obliterans	0.064	0.100	0.102	0.088	0.076	0.082	.....	.....	.....	.....

TABLE 5.—BLOOD SUGAR TESTS IN HEALTHY NORMAL CONTROLS

Case	Fasting Level, per Cent.	After Sugar Ingestion				Sugar Tolerance
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	
H. W. ....	0.120	0.168	0.150	.....	0.120	Normal
M. D. ....	0.118	0.159	0.140	0.120	0.115	Normal
S. L. ....	0.140	0.175	0.142	0.130	.....	Normal
A. Y. ....	0.137	0.171	0.145	0.128	.....	Normal

In the two patients diagnosed clinically as simple goiter (Table 4), note the normal sugar curves: no hyperglycemia and normal assimilation time. The patient whose case was diagnosed clinically as hypopituitarism, showed a low fasting level, a delayed assimilation and normal tolerance. The patient with endarteritis showed hypoglycemia, a very low peak and slight delay in assimilation.

In Table 5 note the two fasting levels higher than normal. As already mentioned, the fact that the controls were laboratory technicians actively engaged a whole hour previous to the test probably accounts for the higher figures. My own fasting level is 0.095 per cent.

The group analyzed in Table 6 represents six patients discharged or transferred from the hospital with a clinical diagnosis of exoph-

thalmic goiter. All of the patients' blood showed hypoglycemia, sugar curves with low peaks and normal assimilation time. On the results of this test, hypofunction of the thyroid is suggested, but, of course, a diagnosis could not be advanced. Hypothyroidism may be present in exophthalmic goiter. Reference to this fact will be referred to in the discussion.

#### RESULTS OF THE EPINEPHRIN SENSITIVE TEST

According to Goetsch, "in states of hyperthyroidism, there is a hypersensitiveness to adrenalin, . . . administered hypodermically . . . which hypersensitiveness is proportional . . . to the degree of hyperthyroidism present . . . In a so-called positive reaction, . . . a subcutaneous dose of adrenalin is characterized by an early rise in blood pressure, and pulse, varying from 10 to 50 and normally proportional to the degree of toxicity present. . . . There is also moderate exaggeration of the symptoms, such as asthenia, tremor, throbbing, vasomotor changes, apprehension and nervousness."

TABLE 6.—BLOOD SUGAR TESTS ON CASES DIAGNOSED EXOPHTHALMIC GOITER, WITH PROBABLE HYPOFUNCTION

Case	Fasting Level, per Cent.	After Sugar Ingestion				
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.
Z. W. ....	0.072	.....	0.095	0.065	0.050	0.073
D. G. ....	0.070	0.083	0.095	0.073	0.067	0.075
C. R. ....	0.070	0.050	0.055	0.105	0.060	0.064
A. S. ....	0.063	0.116	0.087	0.081	0.070	0.060
M. A. ....	0.055	0.055	0.052	0.075	0.075	0.045
B. J. ....	0.077	0.080	0.084	0.082	0.085	0.077

The record of a positive epinephrin test on one of the patients is shown in Table 7.

The results recorded in Table 8 do not appear to establish the Goetsch epinephrin sensitive test as infallible in the diagnosis of hyperfunctional activity of the thyroid gland. It proved negative in a case of frankly toxic exophthalmic goiter and positive in two cases of functional cardiac disorder. A positive reaction seems more likely to be a measure of the sensitization of the sympathetic or vegetative nervous system, whatever the exciting cause, rather than a hyperfunction of the thyroid gland. The presence or absence of glycosuria, within two hours following the injection of 0.5 c.c. of a 1:1,000 epinephrin solution, when studied in conjunction with the pulse and blood pressure, is a factor to be considered in a diagnosis based on this test. Two of the above five cases with positive epinephrin tests on the thyroid group had an associated glycosuria. There was no glycosuria with the two positive epinephrin tests in functional cardiac disorder.

TABLE 7.—RESULTS OF EPINEPHRIN TESTS ON PRIVATE J. R. R., COMPANY A, 340TH INFANTRY, NOV. 1, 1918. DIAGNOSIS, EARLY HYPERTHYROIDISM

Nov. 1, 1918 p. m.	Pulse	Res- pira- tion	Blood Pressure S. D.	Symptoms	
				Subjective	Objective
3:35	92	20	140-80	Comfortable; mentally quiet; no fear; no pain; no palpitation; mouth moist	Jugular pulsation and throbbing in neck fairly pronounced. Hands cool, moist. Face slightly flushed; no cyanosis
3:45	91	20	140-76		
3:50	Urine collected for sugar test			(Urine negative for sugar)	
4:00	Epinephrin, 7½ min., 1:1,000 subcutaneously				
4:05	110	18	150-66	Throbbing in epigastrium and arm. Pain in left arm	Throbbing more prominent in vessels of neck. Throbbing in epigastrium
4:15	112	18	170-60	Throbbing or pumping not so evident. Thrill felt over entire body	Throbbing more prominent in neck and epigastrium. Pupils dilated. Slight cyanosis of hands. Feet cool
4:20	112	22	140-60	Thrill still felt through body. Mouth feels moderately dry	As before. Hands cool and moist. Throbbing still prominent
4:25	116	20	161-50	Not uncomfortable	Throbbing about same. Pupils still dilated
4:30	116	20	160-50	Slight pain on breathing, precordial. Feels warm in face	Slight epigastric pulsation. Feet cold. Hands cool
4:35	120	22	146-52	About the same	As above
4:40	120	18	150-80	Pain in left arm radiating from site of hypodermic injection	Skin of arm at site of injection white, blanched. Hands cool, moist
4:40	Urine collected for sugar test			(Urine positive for sugar)	
4:45	112	22	150-80	Feels about same	As above. Pupils still dilated
4:50	120	16	150-80	No change	Pulsation in arm and epigastrium much diminished
4:55	116	20	150-80	Throat feels dry. Otherwise feels about normal. Arm feels sore at injection site	Pulsation in neck as before test. Pupils still dilated
5:00	108	16	142-80	About same	Epigastric pulsation hardly perceptible. Otherwise as above
5:30	Urine collected for sugar test			(Urine, trace of sugar)	

Interpretation: Test reveals a moderate hypersensitiveness to epinephrin, with a moderate exaggeration of symptoms, with slight glycosuria.

TABLE 8.—THE EPINEPHRIN TEST IN CASES OF THYROID AND FUNCTIONAL CARDIAC DISORDERS

Case	Diagnosis	Result	Glycosuria
A. L.	Mild hyperthyroidism.....	Positive	
L. C.	Mild hyperthyroidism.....	Negative	
R. J.	Mild hyperthyroidism.....	Positive	Trace
V. H.	Mild hyperthyroidism.....	Positive	None
R. H.	Exophthalmic goiter.....	Positive	
R. B.	Exophthalmic goiter.....	Negative	
D. G.	Exophthalmic goiter.....	Positive	Trace
B. E.	Exophthalmic goiter.....	Positive	
B. F.	Functional cardiac disorder.....	Negative	None
F. M.	Functional cardiac disorder.....	Positive	None
F. C.	Functional cardiac disorder.....	Positive	None
L. F.	Functional cardiac disorder.....	Negative	None

## III. RESULTS OF TESTS FOR NITROGEN LOSS

It has long been established that nitrogen metabolism, in exophthalmic goiter, is increased. There is a nitrogen loss by way of the kidneys and the bowel. Total nitrogen and ammonia nitrogen of the urine were therefore recorded. In line with recent investigations and from a considerable amount of evidence accumulated by Benedict and by Cathcart in 1907 and later by Orr,<sup>4</sup> to show that privation of carbohydrates, or any derangement of its metabolism leads to an excretion of creatin in the urine, creatinin and creatin were therefore estimated.

On account of lack of facilities in weighing diets and measuring the nitrogen intake, the results of nitrogen elimination in the urine is therefore only suggestive. The creatin figures I consider to be more conclusive. All patients were ambulatory, all had the same so-called ward diet: meat once a day, vegetables, bread, butter, milk, coffee, puddings, fruit and occasionally eggs. The urine was collected under exact and proper supervision and preservation.

TABLE 9.—PROTEIN METABOLISM IN THYROID AND FUNCTIONAL CARDIAC DISORDERS

Case	Diagnosis	Urine			
		Total N, Gm.	Ammonia, C.c.	Creatinin, Gm.	Creatin, Mg.
H. T.	Exophthalmic goiter.....	7.29	309	1.0	50
R. B.	Exophthalmic goiter.....	15.80	1,103	1.58	176
B. E.	Exophthalmic goiter.....	10.65	641	2.32	110
L. C.	Mild hyperthyroidism.....	7.30	...	1.25	80
A. L.	Mild hyperthyroidism.....	14.95	584	1.97	30
B. A.	Mild hyperthyroidism.....	11.70	890	1.46	210
R. J.	Mild hyperthyroidism.....	14.92	708	1.82	420
S. D.	Functional cardiac disorders.....	12.00	...	1.21	10
S. F.	Functional cardiac disorders.....	4.59	462	0.69	3
T. V.	Functional cardiac disorders.....	11.18	...	1.45	0
B. F.	Functional cardiac disorders.....	6.94	442	2.10	27

The methods of Folin were employed in the estimation of total nitrogen, creatinin and creatin. The ammonia is expressed in terms of tenth normal acid. The chapter on quantitative analytical methods in Medical War Manual No. 6, U. S. Army, proved a reference handbook of value throughout the investigations.

In Table 9 note the very low (normal) figures for creatin in the four cases of functional cardiac disorder. The four cases of mild hyperthyroidism show an increased creatin output in twenty-four hours. A similar increase in creatin was found in the three goiter cases recorded. The creatinin output did not show a corresponding increase, remaining within normal limits in the three groups examined. For total nitrogen the figures for high output through the kidneys are found in the thyroid groups. The ammonia nitrogen

4. Orr: Biochem. J., October, 1918.

figures for the thyroid groups are also higher than normal. One exophthalmic goiter patient (H. T.) with a comparatively low nitrogen output, also had a rather low blood sugar fasting level, which leads to the assumption that metabolic changes in this patient were at the time not increased. The goiter was of several years duration. Thus, the total nitrogen, creatin and ammonia output in the urine showed higher figures in the thyroid cases.

#### IV. TESTS FOR ACIDOSIS, THE RESULT OF A TOXIC FUNCTIONAL ACTIVITY OF THE THYROID GLAND

The severer symptoms and the more striking stigmata of acute toxic goiter are suggestive of an acid intoxication, with depletion of the blood carbonates; similar in fact to the symptoms observed in the oxybutyric acidosis of diabetes and of the food intoxications in children. The symptoms of toxemia include extreme restlessness, tachycardia, vasomotor changes, tremors, dyspnea, loss of weight and psychic disturbances. Kuriyama<sup>5</sup> produced acidosis in rabbits by thyroid feeding, but had negative results after injections of epinephrin.

*Methods.*—The measure of acidosis was estimated indirectly by Sellards'<sup>6</sup> sodium bicarbonate tolerance test, Folin's, and also Henderson's<sup>7</sup> tests for titratable and total acidity, and by Marriott's<sup>8</sup> test for the alveolar air CO<sub>2</sub> tension.

The sodium bicarbonate tolerance test proved the more applicable to the three groups studied, and revealed a lessened alkalinity of the blood in the thyroid patients. This test should be performed not less than three hours after a meal, as food for an average diet has a tendency to render urine, passed just following a meal, alkaline. According to Sellards,<sup>6</sup> 10 gm. is the average upper level of alkali required for ingestion, in order that the urine may become neutral or alkaline.

Marriott's alveolar air CO<sub>2</sub> test for acidosis was also applied, but results even in the functional cardiac disorders were often found below the normal from 40 to 45 mm. CO<sub>2</sub> tension. It is generally accepted that a decreased CO<sub>2</sub> tension of alveolar air, when found associated with cardiac disorders, is primarily a result of pulmonary-circulatory disturbances. It is not, therefore, the method of choice when applied to cardiac or pulmonary diseases.

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5. Kuriyama, S.: The Influence of Thyroid Feeding on Carbohydrate Feeding, *J. Biol. Chem.* **33**:215 (Jan.) 1918.

6. Sellards, A. W.: *Acidosis*, 1917.

7. Henderson, L. J.: Total Acidity of Urine, *J. Biol. Chem.*, 1911, No. 9, p. 403; also see *War Manual* No. 6.

8. Marriott, W. McK.: A Method for the Determination of the Alveolar Carbon Dioxid Tension, *J. A. M. A.* **66**:1594 (May 20) 1916.

The free (titratable) acidity and the total acidity (the phenol-sulphonephthalein, formaldehyd titration method) are expressed in terms of tenth normal acid: 600 c.c. is high normal for titratable acidity; 1,600 c.c. represents the maximum normal figure for total acidity of the urine.

TABLE 10.—EXAMINATION OF PLASMA CO<sub>2</sub>, ALVEOLAR AIR CO<sub>2</sub>, TENSION AND URINE

Case	Diagnosis	Plasma CO <sub>2</sub> Vol- ume, per Cent.	Alveolar Air CO <sub>2</sub> Tension, Mm.	Urine		
				Sodium Bicar- bonate Toler- ance, Gm.	Titrat- able Acidity, C.c.	Total Acid- ity, C.c.
H. T.	Exophthalmic goiter.....	52	34.0	Over 20	...	1,695
B. E.	Exophthalmic goiter.....	..	28.3	15	516	1,157
D. G.	Exophthalmic goiter.....	..	30.0	10	945	.....
L. C.	Mild hyperthyroidism.....	..	31.3	15	674	.....
A. L.	Mild hyperthyroidism.....	..	33.0	15	613	1,197
B. A.	Mild hyperthyroidism.....	..	31.7	10	1,100	1,990
R. J.	Mild hyperthyroidism.....	..	31.0	20	592	1,300
M. A.	Mild hyperthyroidism.....	..	34.0	15	642	.....
S. D.	Functional cardiac disorder.....	..	36.0	Alkaline	363	.....
S. F.	Functional cardiac disorder.....	..	32.0	5	521	983
T. V.	Functional cardiac disorder.....	..	36.0	10	520	.....
B. F.	Functional cardiac disorder.....	..	31.3	10	294	736
J. J.	Functional cardiac disorder.....	..	40.0	10	...	1,510
F. J.	Functional cardiac disorder.....	..	32.0	5	313	.....

In one exophthalmic goiter patient (Table 10) with apparently a severe toxemia, the plasma CO<sub>2</sub> is recorded as fifty-two volumes per cent. This figure is the upper level of acidosis, and therefore mild in degree. Normal limits of blood plasma CO<sub>2</sub> are from 65 to 75 volumes per cent. Note in the thyroid groups the higher amounts of sodium bicarbonate required to make the urine neutral or alkaline. Tests for titratable and total acidity of the urine give also increased results in the thyroid patients.

CASE 2.—PRIVATE E. B., SEVENTH BATTALION, 153 D. B.

Weight, 147½ pounds; height, 70½ inches; livestock buyer; 24 years of age; married; in service three months. Diagnosis, August 6, heat exhaustion. L. O. D. August 13, exophthalmic goiter. E. P. T. E. August 13, chalazion (left lower lid), E. P. T. E.

Sugar Tolerance Test Blood. 8/15/18 150 pounds weight 1.75 gm. per kilogram; 120 gm. sucrose a.m.	Urine 1.75 gm. per kilo- gram; 120 gm. su- crose	Coagula- tion Time 4½ minutes	Alveolar CO <sub>2</sub> Tension 8/16 28.3 mm. tension Normal 35 to 45 mm.
8:00-1-127 mg. per 100 c.c. before sucrose	8:00 before sucrose—		
8:30-2-134 mg. per 100 c.c. after sucrose	negative Benedict		
9:00-3-162 mg. per 100 c.c. after sucrose	9:00 after sucrose—		
9:30-4-200 mg. per 100 c.c. after sucrose	negative Benedict		
10:00-5-164 mg. per 100 c.c. after sucrose	10:00 after sucrose..		
10:30-6-166 mg. per 100 c.c. after sucrose	negative Benedict		
11:00-7-145 mg. per 100 c.c. after sucrose	11:30 after sucrose—		
11:30-8-135 mg. per 100 c.c. after sucrose	negative Benedict		
12:00-9-135 mg. per 100 c.c. after sucrose			
Poor assimilation for sugar			

Indican	Titration Acid (Urine)	Sodium Bicarbonate Tolerance Test, Urine	Blood Examination	Goetsch Epinephrin Test
9/14 Negative	8/21 Sp. Gr. 1.016 8/28 Amount 516 c.c. N/10 acid (Normal) 9/14 Total acidity, 1,157.7 c.c. N/10	8/27 3.15 urine acid 3.20 5 gm. sodium bicarbonate 3.45 urine acid 3.50 5 gm. sodium bicarbonate 4.15 urine acid 4.20 5 gm. sodium bicarbonate 4.45 urine alkaline	Lymphocytes 29% Large mono- nuclears.... 8% Total..... 37% Normal	8/23 Moderate reaction

Fluoroscopic Examination: Sept. 5, 1918. Thyroid: showed bilateral enlargement (moderate) of thyroid gland. Thymus: no shadow.

Reaction to Typhoid Inoculation: Moderately severe.

Urine: 24 hours.—Total nitrogen, 10.65 gm.; creatinin, 2.32 gm.; creatin, 0.105 gm.

This is a complete record of clinical and laboratory tests such as were made on many of the patients studied.

#### DISCUSSION

In MacCurdy's book, "War Neuroses,"<sup>9</sup> the general conclusion is expressed that most of the cases in soldiers of "disordered action of the heart" are not neurotic in the narrow sense, but are to be regarded as of organic origin, either from some endocrine disorder, disturbance of the vegetative nervous system, or involvement of the inherent cardiac mechanism. However, as pointed out above, it is agreed with Addis and Kerr<sup>10</sup> that enlargement of the thyroid in some patients with a cardiac neurosis may be incidental and not causative.

The above studies represent an effort to detect early hyperthyroidism in patients classified among the heart neuroses cases. I believe that four or five patients, by means of laboratory tests, did show hyperfunctional activity of the thyroid.

The presence of disordered thyroid function has been previously recognized and reported by medical officers since the outbreak of the great war. Beebe<sup>11</sup> asserts that many cases of "soldier's heart," are in reality cases of hyperthyroidism. Brooks<sup>12</sup> reported a large number of hyperthyroid disorder developing among soldiers at Camp Upton. Ewing<sup>13</sup> points out that a persistent thymus may often be the underlying factor responsible for the "irritable heart" and "irritable thyroid" of soldiers. Other writers give the impression that thyroid enlargement is almost constantly associated with the functional cardiac disorder syndrome. It has been a new experience to find disturbance of the thyroid so prevalent in young men. Should appropriate metabolic tests have been performed upon this seemingly large thyroid disorder group, the great majority would have proved simple physiological enlargement, nontoxic and compensatory, following upon overstrain.

9. MacCurdy, J. T.: War Neuroses, New York, G. P. Putnam's Sons, 1918.

10. Addis, Thomas, and Kerr, W. J.: Relative Frequency in Recruits with and without Thyroid Enlargement, etc., Arch. Int. Med. **23**:316 (March) 1919.

11. Beebe, S. P.: Med. Rec. **93**:337 (Feb. 9) 1918.

12. Brooks, Harlow: Am. J. M. Sc. **156**:726 (Nov.) 1918.

13. Ewing, J.: J. A. M. A. **71**:1525 (Nov. 9) 1918.

It is impossible, therefore, to entirely concur with the numerous investigators who have based a diagnosis of hyperthyroidism on symptoms and signs of vasomotor or nervous instability, symptoms and signs that other workers have unreservedly ascribed to a heart neurosis, calling the syndrome "neurocirculatory asthenia, irritable heart, effort syndrome, constitutional inferiority or cardiac defect functional."

One great fact that has clarified our understanding of thyroid derangement, is the recognition that exophthalmic goiter does not mean hyperthyroidism; that even toxic exophthalmic goiter symptoms frequently occur with hypothyroidism, in 23 per cent. of cases, according to Bertine.<sup>14</sup> Thyroid deficiency is present not only in myxedema, but at puberty, during pregnancy and following overstrain.

Therefore, hypertrophied thyroid, or goiter, does not mean hyperfunction. Hyperthyroidism is a misnomer, and a new word is needed to express the metabolic derangement caused by hyperfunctional activity of the thyroid.

An increase in basal metabolism, a nitrogen loss and hyperglycemia are recognized laboratory findings in hyperthyroidism. Creatinuria is present in exophthalmic goiter and in hyperthyroidism.<sup>15</sup> The following outline is my understanding of the present accepted theory of hyperthyroidism and hypothyroidism.

Disorder	Pathology	Type	Effect	Associated
Hyperthyroidism	Excess of normal hormone	Enlarged	May be toxic	May have exophthalmus
Hyperthyroidism	Excess of unsynthesized hormone	May be small	May be toxic	May have exophthalmus
Hypothyroidism	Deficiency of normal hormone	May be large	Nontoxic	No exophthalmus
Hypothyroidism	Small amount abnormal hormone	Enlarged or small	Toxic	May have exophthalmus

*Creatinuria.*—Though creatinin is a normal, and for each individual a fairly constant constituent of the urine, creatinuria, with few exceptions, is the result of a disturbance of metabolism. I agree with Mendel and Rose,<sup>16</sup> Orr and others, that the output of creatin is inversely proportional to the amount of carbohydrates ingested. It is increased also in starvation. Creatin is mostly endogenous, namely, from the tissues, but its loss in the urine depends on a derangement in carbohydrate, rather than in protein metabolism.

The intimate correlation and interaction of the glands of internal secretion, actively assisting in the direct control of the body metab-

14. Bertine, E.: Med. Rec. **90**:895 (Nov. 18) 1916.

15. Denis, W.: J. Biol. Chem. **30**:47 (May) 1917; **30**:189 (June) 1917; **31**:561 (Sept.) 1917.

16. Mendel, L. B., and Rose, W. C.: J. Biol. Chem. **10**:213, 1912.

olism in growth and repair, makes difficult the localization of functional disorders in the endocrine gland system. The recognized fact that the etiology of heart neuroses is still a big problem, and that the early diagnosis of hyperthyroidism by symptoms alone is almost an impossibility, should prompt the clinician or surgeon familiar with the newer laboratory and clinical tests to study his functional cardiac and endocrine disorder patients with the aid of these analytical methods.

#### SUMMARY

1. The laboratory affords the most reliable means toward the recognition of early hyperthyroidism.

2. Early hyperthyroidism may be the cause of a heart neurosis. Simple, physiologic, goiter may be found associated with functional disorder of the heart, without evidence of hyperthyroidism.

3. The sugar tolerance test seems an important aid in the detection of borderline cases or early hyperthyroidism.

4. The epinephrin test did not prove, in the study of the cardiac neuroses, diagnostic of hyperthyroidism. It seemed rather an index of the sensitization of the sympathetic nervous system. Its value as a diagnostic test is increased when blood and urinary sugar estimations are recorded with pulse rate and blood pressure. Intramuscular injections gave best results.

5. Tests for nitrogen loss and acidosis seemed suggestive as aids in the diagnosis of toxic hyperthyroidism. Further studies are being made to discover if borderline cases or early hyperthyroidism reveal such changes. Creatinuria did seem present in the thyroid disorder group, and when taken in conjunction with the other tests, was of value in the diagnosis of early hyperthyroidism.

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# THE CONTROL OF ACIDOSIS IN THE TREATMENT OF DIABETES \*

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## INTRODUCTION

During the past five years marked advances have been made in the treatment of diabetes, due largely to the introduction by Allen of the "fasting method." In the practical application of this method of treatment the patient is fasted until glycosuria disappears; and subsequent to the initial fast, fasting is employed to such an extent as is necessary to aid in keeping the patient free from glycosuria. In other words, the most important and significant sign or symptom by which the therapeutic regime is regulated is the presence or absence of sugar in the urine. Allen, however, has emphasized the fact that in diabetes a disturbance of the entire metabolic mechanism of the body is present, and that the presence or absence of glycosuria at any given time is but a crude test of the state of that function, though practically it is the best test available. In the latest publication,<sup>1</sup> stress is laid on the importance of the state of the blood sugar, and attention is also drawn to the importance of acidosis.

The questions of the nature of acidosis and the relationship between changes in alkaline reserve and clinical symptoms have been discussed in previous papers from this Hospital (Van Slyke and Cullen;<sup>2</sup> Stillman, Van Slyke, Cullen and Fitz;<sup>3</sup> Fitz,<sup>4</sup> 1917; Palmer and Van Slyke<sup>5</sup>). Suffice it to say that although other factors, including, perhaps, unknown toxins, can also cause diabetic collapse (Fitz<sup>4</sup>), as a rule, the severity of the clinical symptoms parallels the fall in plasma bicarbonate; moreover, the plasma bicarbonate begins to fall before the symptoms appear.

The introduction of more exact methods for the study of acidosis, in particular, methods for determining blood plasma bicarbonate, and the opportunity for combined clinical and laboratory studies on a group

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\* From the Hospital of the Rockefeller Institute for Medical Research, New York.

1. Allen, F. M., Stillman, E., and Fitz, R.: New York, Monograph of the Rockefeller Institute, 1919, No. 11.

2. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **30**:289, 347, 389, 401, 405 (June) 1917.

3. Stillman, E., Van Slyke, D. D., Cullen, G. E., and Fitz, R.: J. Biol. Chem. **30**:405 (June) 1917.

4. Fitz, R.: Proc. Assn. Am. Phys. **32**:155, 1917; **30**:389, 405 (June) 1917.

5. Palmer, W. W., and Van Slyke, D. D.: J. Biol. Chem. **32**:499 (Dec.) 1917.

of patients, selected chiefly for the severity of their diabetes, have resulted in the gradual development in this clinic of systematic procedures, first, for ascertaining the individual reactions of the patient in regard not only to his carbohydrate tolerance, but also his tendency toward acidosis, and second, for guiding the treatment by the metabolic reactions that have been ascertained. The present paper is an outline of these procedures.

#### LABORATORY CONTROL

The minimum laboratory control with which satisfactory results may be considered possible consists of qualitative glucose and acetoacetic acid tests on the daily urine samples, with determinations of plasma bicarbonate when the urine shows a strong test for acetoacetic acid, or when any of the clinical signs are unfavorable. The symptoms of incipient acidosis are extremely variable; they may include indefinite malaise, headache, slight nausea, neuralgic pains, or almost any abnormal symptom. Consequently, the slightest unfavorable clinical sign at any stage of treatment should be taken as an indication for determining the plasma bicarbonate.

It is desirable, also, especially for patients whose condition is uncertain or who are being put on a new regimen, to determine quantitatively the blood sugar and the daily excretion of sugar and acetone bodies in order to follow the progressive effect of the treatment. We have usually determined the blood sugar whenever blood was drawn for bicarbonate estimation.<sup>6</sup>

#### OUTLINE OF ROUTINE

For the most expeditious creation and maintenance of an aglycosuric and aketogenic state, the routine evolved in applying the prin-

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6. The methods used in this clinic have been the following: Blood plasma bicarbonate: CO<sub>2</sub> capacity method, Van Slyke and Cullen<sup>2</sup> (the titration method of Van Slyke, Stillman and Cullen<sup>7</sup> was not available at the time these observations were made). Blood sugar: Lewis and Benedict method, as modified by Myers and Bailey.<sup>8</sup> Urinary sugar: qualitative, Benedict;<sup>9</sup> quantitative, Benedict (1911). Acetone bodies in urine: qualitative, the well known ferric chlorid test of Gerhardt, described in all laboratory manuals; quantitative, Van Slyke.<sup>10</sup> Acetone bodies in blood: quantitative, Van Slyke and Fitz.<sup>11</sup> Titrable acids in urine: Folin.<sup>12</sup> Ammonia in urine: Van Slyke and Cullen.<sup>13</sup>

7. Van Slyke, D. D., Stillman, E., and Cullen, G. E.: *J. Biol. Chem.* **38**: 167 (May) 1919.

8. Myers, V. C., and Bailey, C. V.: *J. Biol. Chem.* **24**:147 (Feb.) 1916.

9. Benedict, S. R.: *J. Biol. Chem.* **5**:485, 1908; **9**:57, 1911.

10. Van Slyke, D. D.: *J. Biol. Chem.* **32**:455 (Dec.) 1917.

11. Van Slyke, D. D., and Fitz, R.: *J. Biol. Chem.* **32**:495 (Dec.) 1917; **37**:551 (April) 1919.

12. Folin, O.: *Am. J. Physiol.* **9**:265, 1903.

13. Van Slyke, D. D., and Cullen, G. E.: *J. Biol. Chem.* **19**:211, 1914; **24**:117 (Feb.) 1916.

ciples of the fasting treatment in this hospital may be outlined as follows:

1. A preliminary observation diet.
2. The creation of the aglycosuric and aketogenic state by either continuous or intermittent fast.
3. Estimation of the individual carbohydrate tolerance.
4. Determination of the maintenance diet.
5. Final observation period.

The significance, according to our experience, of acidosis in each stage of the treatment and its consideration in modifying the treatment are indicated in the following pages.

1. *The Preliminary Observation Diet.*—On admission to the hospital patients not suffering from acidosis have been placed on the following observation diet in order to ascertain their behavior under standardized conditions (See Table 4).

TABLE 1.—OBSERVATION DIET

Protein, Gm. 1.5 per kilogram	Carbohydrate, Gm.* 10-25	Fat, Gm. Sufficient to bring total calories to 35 per kilogram body weight
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\* Carbohydrate in the form of green vegetables only, from 10 to 25 gm. according to apparent severity of the case.

Acidosis of the moderately severe or severe type (plasma bicarbonate  $\text{CO}_2$  below 40 volumes per cent.) has been considered the one contraindication to placing the patient on the observation diet and maintaining him on it for the usual length of time. Such patients have been put on fasting directly on admission to the hospital as requiring immediate and active treatment (Table 5).

2. *Creation of the Aglycosuric State by Continuous or Intermittent Fast.*—After the period of the observation diet, the patient is placed on a continuous fast (Tables 4, 5 and 6). This is continued until the patient is rendered aglycosuric unless acidosis develops. By the continuous fast is meant absolute abstinence from all foods containing any demonstrable amount of carbohydrate, protein or fat, continued without interruption until the patient has been made sugar free for twenty-four hours. In our series of cases this has required from two to eleven days. Fluids, in the form of clear soup, coffee and water, are taken daily in a total amount of at least from 1,500 to 2,000 c.c.

In occasional instances (one out of sixteen in our cases which were, of course, selected for their severity) continuous fasting has resulted in the development of dangerous acidosis. Consequently, patients on continuous fasts have been watched carefully for this development. The clinical symptoms of incipient acidosis have been found to vary so extremely that any local or general malaise has come to be looked on with suspicion. The only reliable tests have been found to be those of the laboratory. It seems well to emphasize here that we have come

to believe that during the fasts accurate daily determinations of the plasma bicarbonate should be performed to obviate a certain percentage of fatalities.

In the cases developing or retaining acidosis on the continuous fast (Table 7), as shown by plasma bicarbonate much below normal, continuous fast has been changed to the intermittent fast. Its object is the same as that of the continuous fast—namely, the creation of an aglycosuric state—and its substitution has been made solely when acidosis has resulted from the more expeditious continuous method.

By the intermittent fast is meant an absolute fast, for periods of time depending on the reaction of the patient, from all foods containing any demonstrable amount of carbohydrate, protein, or fat, the fasting periods being interrupted by intervals of diets low in caloric value (see Table 7 and accompanying description).

The manner in which the continuous and intermittent fasting treatments have been applied has been governed by the state and behavior of the bicarbonate reserve of the patient's blood.

(a) In cases with no acidosis or only mild acidosis, as determined before the institution of fasting, a moderate fall in the plasma bicarbonate has been permitted before the continuous fast was abandoned for the intermittent.

(b) If the existing acidosis was moderately severe (plasma bicarbonate  $\text{CO}_2$  of from 30 to 40 volume per cent.) even a drop of two or three volume per cent. in bicarbonate, especially if the fall was progressive, was sufficient to cause interruption of the fast.

(c) In cases in which the bicarbonate determination showed a severe acidosis (plasma bicarbonate  $\text{CO}_2$  below 30 volume per cent.) active treatment was instituted as follows:

Sodium bicarbonate: 3 gm. per hour, dissolved in cold water, until the bicarbonate of the blood became normal.

Fluids: Forced to the limit, but not to the extent to cause nausea; it has been attempted to give about 5,000 c.c. of fluid during the twenty-four hours.

Coffee: Clear, very strong coffee has been given to stimulate the renal action of patients suffering from severe acidosis. As much as from 1,200 to 1,500 c.c. of coffee has been given during the day.

Whisky: No beneficial effect on the acidosis has been obtained from giving alcohol, and it has apparently nauseated in some instances; therefore, the use of whisky as a therapeutic measure for acidosis has been discontinued in this hospital.

Catharsis: Active catharsis by calomel and salts, together with high colon irrigations until the washings are returned without fecal matter, has been instituted. We have no exact data as to the part which this

treatment has had in ameliorating the acidosis, but clinically the effects have seemed to be beneficial.

Diet: Continuous fasting has been applied directly on admission. If from six to twelve hours' fasting, together with the above treatment, did not cause an increase in the plasma bicarbonate, light feeding was begun. It was thought theoretically correct that such feeding should be principally protein, as carbohydrate in such cases is not burnt, and could only add to the severity of the diabetes, while fat leads to the formation of ketone bodies and consequent direct increase in acidosis. Therefore, from 600 to 800 calories have been given in the form of eggs and lean meat (see Table 7).

In the treatment of acidosis we have found that nausea is the condition above all others to be avoided, because if it becomes uncontrollable, successful treatment of the acidosis becomes nearly impossible. Nausea may be produced by any one of the above mentioned measures — bicarbonate therapy, the forcing of fluids, catharsis, the institution of fasting, or the institution of feeding. Experience has taught us that close clinical observation and frequent laboratory tests can, in the great majority of cases, prevent the development of nausea, if at the first sign of any intensification of it the offending factor in the treatment, whether it be forced fluids, bicarbonate, fasting or feeding, be discontinued until the symptoms of nausea disappear.

The statements bearing on the degree of acidosis and the laboratory indications for changing from continuous to intermittent fasting are summarized in Table 2.

TABLE 2.—DEGREE OF ACIDOSIS AND LABORATORY INDICATIONS FOR CHANGING FROM CONTINUOUS TO INTERMITTENT FASTING

Degree of Acidosis	CO <sub>2</sub> Combining with 100 C.e. of Blood Plasma, C.e.	Acid Excretion* N/10 NH <sub>3</sub> + Acid Kg. Body Weight C.e.	Drop of CO <sub>2</sub> Permitted before Interrupting Fast, C.e.
No acidosis.....	Over 53	0 to 27	To 45
Mild acidosis.....	53 to 40	27 to 65	Drop of 10 to 5
Moderately severe acidosis	40 to 30	27 to 100	Drop of 3 to 2
Severe acidosis.....	Below 30	Over 100	Fast interrupted after 6 to 12 hours unless CO <sub>2</sub> rises with treatment outlined above

\* Concerning the interpretation of the relationship of the urinary acid excretion figure, N/10 NH<sub>3</sub> + titratable acid

, to severity of acidosis, the reader is referred to the discussion in paper X of the Studies of Acidosis (Van Slyke, 1918). The ordinary correspondence between these figures and the degree of acidosis is indicated by the table.

*Estimation of the Individual Carbohydrate Tolerance on a Diet of Green Vegetables Alone.*—After the patient has been made aglycosuric by the fasting method and has remained aglycosuric for twenty-four hours, he has been placed on a graduated carbohydrate tolerance test. This test has been performed by giving a diet comprised of green vegetables alone, starting the test

with green vegetables containing 10 gm. of carbohydrate and increasing the amount of carbohydrate 10 gm. each day, until glycosuria results (Tables 4, 5, 6 and 7). Occasionally a trace of sugar has been found to occur in the urine during the first days of the test. This not infrequently has been found to clear up without fasting, and the patients have frequently shown an ability to metabolize many times the amount of carbohydrate that the first sugar reaction seemed to indicate was the limit of their tolerance. Therefore, on the first appearance of glycosuria we have continued the same amount of carbohydrate for another twenty-four hours; if, at the end of this time, there was cessation of the sugar excretion, the test was continued, the carbohydrate food being increased daily until glycosuria appeared on two successive days. This point we have considered as indicating the carbohydrate tolerance for the individual under observation. Fasting was then again instituted until the patient had become sugar free for twenty-four hours. The determination of the maintenance diet was then begun.

The carbohydrate tolerance test establishes a basis for comparison with later tests, whereby the progress of the patient can be determined, and also affords a basis for the initial maintenance diet as described below.

In cases in which although acidosis has been benefited by fasting, but has not been entirely eradicated, the carbohydrate test diet has usually raised the blood bicarbonate to a full normal. The ketonuria, also, which has usually accompanied subnormal blood bicarbonate, has been diminished or entirely stopped. The green vegetable diet may be considered almost a specific for mild acidosis. (Note its effect in Tables 4, 5 and 6 in raising plasma bicarbonate and abolishing the ferric chlorid reaction for acetoacetic acid in the urine.)

*Determination of the Maintenance Diet.*—By the maintenance diet is meant a mixed diet, which is as near a normal diet as can be tolerated without glycosuria and with fully normal plasma bicarbonate. After having made the patient aglycosuric and having determined the carbohydrate tolerance, it has been our custom to place him on a trial maintenance diet (Table 3).

TABLE 3.—THE TRIAL MAINTENANCE DIET

Carbohydrate	Per 24 Hours	
	Protein	Fat
One tenth the amount tolerated on the carbohydrate tolerance test	1.5 gm. per kg. body weight	Sufficient to bring the total caloric value of the diet to 35 calories per kg. of body weight

If the diet was well tolerated and the patient appeared to need more, an increase was made in the constituents of the diet which appeared to be most needed. Care was taken that only one of the three constituents, either the fat, the protein, or the carbohydrate, was increased at a time and in a gradual systematic manner, so that should glycosuria or ketonuria result the offending food could be recognized and reduced.

Urinary tests for glucose and ketones have been made daily, while the plasma bicarbonate has been determined at least once a week, and as often after as the condition and symptoms of the patient rendered advisable (see p. 446).

When either glycosuria, definite ketonuria, or significant fall in plasma bicarbonate occurred on the maintenance diet, the patient has been put on the so-called minimum maintenance diet, which was made up exactly as the maintenance diet, except that the fat was cut down so that the patient received only twenty-five calories per kilogram body weight instead of thirty-five. Prolonged feeding (for from four to twelve weeks) of a diet of such low caloric content has frequently resulted in increased food tolerance, so that the patient could finally take the maintenance or even more than the maintenance diet. When it has been found that it was impossible to create such a tolerance, patients have been discharged on the lower diet.

If at the end of two weeks on the finally chosen maintenance diet, there has been no indication of glycosuria, no significant increase in the glycemia, and the plasma bicarbonate remains stable at a fully normal level, one may feel fairly secure that the patient in question is tolerant of the maintenance diet.

#### EXAMPLES OF RESULTS WITH DIFFERENT TYPES OF DIABETICS

Tables 4, 5, 6 and 7 exemplify the results obtained with patients belonging to the four groups previously described by the author (Stillman<sup>14</sup>). These groups are marked by characteristic differences in their tendencies toward acidosis which are briefly summarized as follows:

**GROUP 1—46.8 PER CENT. OF OUR CASES.**—No tendency to acidosis, either on fast or ordinary diet, regardless of degree of glycosuria.

**Treatment:** Made aglycosuric without danger by continuous fast. Can usually be made to tolerate fairly high calory diet without glycosuria or ketonuria. Easiest group to handle. Best prognosis.

**GROUP 2—32.3 PER CENT. OF OUR CASES.**—Received in condition of moderate or severe acidosis (plasma bicarbonate  $\text{CO}_2$  below 40 volume per cent.), which clears up on fast.

**Treatment:** Made free of glycosuria and acidosis by continuous fast. A tendency toward acidosis is present, and the safely tolerated maintenance diet is usually lower than in Group 1.

**GROUP 3—14.5 PER CENT. OF OUR CASES.**—Tendency to slight acidosis (sub-normal plasma bicarbonate) on any but most carefully chosen diet. Acidosis not increased by fasting.

**Treatment:** Glycosuria removed by continuous fast. Tolerated maintenance diet variable. Usually there is a tendency toward acidosis which may become acute on any improper diet.

**GROUP 4—6.4 PER CENT. OF OUR CASES.**—Either develop or retain severe acidosis (plasma bicarbonate  $\text{CO}_2$  below 30 volume per cent.) when fasted to attain the aglycosuric state. This is incomparably more severe than the mild acidosis observed as a rule, when normal individuals are fasted, and may rapidly become fatal unless the fall in plasma bicarbonate is checked.

**Treatment:** Continuous fast must be given up for intermittent fast (described below). As in Group 2, the presence of a tendency toward acidosis

TABLE 4.—DIETARY RECORD OF CASE 2234, GROUP 1

Date, 1916	Day of Obser- vation	Body Weight, Kg.	Diet			Dextrose		Evidence of Acidosis					NaHCO <sub>3</sub> by Mouth	
			C. H., Gm.	Protein, Gm.	Fat, Gm.	Total Diet, Calories	Urine, Gm.	Blood, per Cent.	Urine					
									N/10 NH <sub>3</sub> C.c.	N/10 Acid C.c.	N/10 NH <sub>3</sub> + N/10 Acid C.c.	Kg. Body Weight, C.c.		Blood: CO <sub>2</sub> Com- bined with 100 C.c. Plasma, C.c.
Jan. 25	1	50.4	10	60.0	130	1,490	3.25 Trace	....						
26	2	50.8	60	60.0	130	1,490	2.55	....						
27	3	50.2	60	60.0	130	1,490	Trace	0.17		218	473	9.5	61.0	
28	4	49.8		Fast			Negative	...						
29	5	49.8		Fast			Negative	....						
30	6	49.6		Fast			Negative	....						
31	7	48.4		Fast			Negative	....						
Feb. 1	8	47.8	10	4.0	0.3	60		....						
2	9	48.0	20	7.5	1.0	120		....						
3	10	48.0	30	10.5	1.9	180		0.15						
4	11	48.2	40	14.0	2.2	240		0.14						
5	12	48.4	50	17.5	2.4	300		0.11		204	346	7.2	65.5	
6	13	48.6	60	20.0	3.1	355	Trace	....						
7	14	48.0	70	23.0	4.6	425	Negative	0.10						
8	15	48.0	80	24.0	4.8	470	Negative	0.12						
9	16	48.2	90	31.0	5.1	545	Negative	0.09						
10	17	48.4	100	31.5	5.0	585	Negative	....						
11	18	48.6	110	34.5	5.5	645	Negative	0.18						
12	19	48.8	120	37.0	6.9	705	Negative	....						
13	20	48.2	130	39.0	7.0	755	Negative	0.11						
14	21	48.6	140	39.5	6.3	795	Negative	0.18						
15	22	48.8	150	43.5	7.0	860	Negative	....						
16	23	49.2	115	31.0	3.3	615	Negative	0.11		71	104	2.1	71.1	

TABLE 5.—DIETARY RECORD OF CASE 2686, CASE 2

Date, 1916	Day of Observation	Body Weight, kg.	Diet			Dextrose	Evidence of Acidosis					NaHCO <sub>3</sub> by Mouth		
			C. H., Gm.	Protein, Gm.	Fat, Gm.		Total Diet, Calories	Urine, Gm.	Blood, per Cent.	24 Hour Urine				
										N/10 NH <sub>3</sub> C.e.	N/10 Acid C.e.		N/10 NH <sub>3</sub> + N/10 Acid C.e.	N/10 NH <sub>3</sub> + Acid Weight, C.e.
Feb. 22	1	...		Fast*			23.0*	0.27		*	*	*	12.2	45
23	2	27.8		Fast			42.0	0.38		835	2,850	102	26.8	50
24	3	26.0		Fast	0.4	60	24.5	0.32					38.3	30
25	4	25.4		Fast	1.0	125	21.0	0.28					40.4	30
26	5	25.0		Fast	1.0	130	12.0	0.26					46.0	20
27	6	25.2		Fast	1.5	210	12.0	0.25					...	15
28	7	25.4		Fast	0.4	30	5.5	0.25					...	
29	8	25.2		Fast	0.4	30	Trace	0.21					...	
Mar. 1	9	25.2		Fast	0.4	60	Negative	0.21					48.7	
	10	25.0	10	3.9	1.0	125	Trace	0.20					43.0	
	11	25.6	20	8.6	1.0	130	Slight	0.20						
	12	26.6	20	8.6	1.0	130	Trace	...						
	13	28.0	25	10.0	1.0	150	Trace	...						
	14	30.0	25	10.0	1.0	150	Trace	0.22						
	15	31.4	25	10.0	1.0	150	Trace	...						
	16	31.8	30	11.5	1.3	180	Trace	0.26						
	17	31.8	35	13.0	1.5	210	Trace	...						
	18	31.6	8.8†	3.3	0.4	50	Trace	0.23						
19	30.4		Fast			Negative	...							
20	30.0	5	1.5	0.2	25	Negative	...							
21	29.8	10	3.8	0.4	60	Negative	...							
22	29.8	20	7.7	0.8	120	Negative	...							
23	29.4	20	8.6	0.9	125	Negative	...							
24	28.0	30	11.3	1.4	180	Negative	...							
25	28.4	40	14.5	1.8	240	Negative	...							
26	28.4	50	18.1	2.2	300	Negative	...							
27	28.6	60	21.3	2.5	355	Negative	...							
28	27.6	70	24.3	2.7	410	Negative	...							
29	26.4	80	27.3	3.2	470	Negative	...							
30	26.0	90	29.9	4.5	530	Negative	...							
31	26.0	100	33.9	6.1	605	Trace	...							
32	25.2	100	33.9	6.1	605	Trace	...							
33	25.0	110	36.0	6.8	660	Trace	...							
34	25.0		Fast			Negative	...							
35	25.2	15	40.0	61.5	795	Negative	...							
27	35	25.2	15	40.0	83.4	Negative	...							
28	36	25.6			1,000	Negative	...							

\* Observation day of 11 hours.

† Fast two meals.

TABLE 6.—DIETARY RECORD OF CASE 2480, GROUP 3

Date, 1916	Day of Observation	Body Weight, kg.	Diet			Dextrose		Evidence of Acidosis					NaHCO <sub>3</sub> by Mouth	
			C. H., Gm.	Protein, Gm.	Fat, Gm.	Total Diet, Calories	Urine, Gm.	Blood, per Cent.	24 Hour Urine					
									N/10 NH <sub>3</sub> C.c.	N/10 Acid C.c.	N/10 NH <sub>3</sub> + N/10 Acid C.c.	N/10 NH <sub>3</sub> + Kg. Body Weight, C.c.		Blood: CO <sub>2</sub> Com- bined with 100 C.c. Plasma, C.c.
Oct. 15	1	48.4	3.5	26.8	92.7	985	Heavy	0.42						
16	2	47.6	5.0	100.0	166.0	2,000	Heavy	....						44.5
17	3	47.6		Fast			Heavy	....	—	—	—	—	—	
18	4	47.9		Fast			Heavy	....	—	—	—	—	—	
19	5	47.4		Fast			Heavy	....	—	—	—	—	—	
20	6	45.5		Fast			Heavy	....	—	—	—	—	—	
21	7	45.5		Fast			Heavy	0.38	...	...	...	....	...	
22	8	45.4		Fast			Heavy	....	...	...	...	....	...	53.2
23	9	45.4		Fast			Heavy	....	...	...	...	....	...	50.4
24	10	45.2		Fast			Moderate	0.27	...	...	...	....	...	
25	11	45.4		Fast			Slight	....	...	...	...	....	...	
26	12	45.3	10	3.5	0.5	60	Negative	0.38	368	151	519	11	47.8	
27	13	46.1	30	8.0	1.0	125	Negative	0.32	...	...	...	....	...	46.6
28	14	46.5	30	11.1	1.7	185	Negative	0.27	298	101	393	9	47.5	
29	15	46.9	40	15.9	2.0	250	Negative	0.24	500	92	592	13	57.9	
30	16	47.2	40	15.9	2.0	250	Trace	0.40	296	82	378	8	56.5	
31	17	47.2	50	17.8	5.8	315	Negative	0.23	186	31	167	3	54.4	
Nov. 1	18	47.0	60	20.0	4.6	375	Negative	....	...	...	...	....	...	53.5
2	19	47.8	60	20.0	4.0	365	Trace	0.14	...	...	...	....	...	
3	20	47.8	70	23.0	4.6	425	Negative	....	...	...	...	....	...	57.1
4	21	47.9	80	26.3	5.7	485	Negative	0.32	...	...	...	....	...	
5	22	47.6	90	27.7	6.6	545	Trace	....	...	...	...	....	...	
6	23	47.6	25*	10.0	1.2	155	Slight	....	...	...	...	....	...	
7	24	46.8		Fast			Negative	....	...	...	...	....	...	
8	25	47.8	5	75.0	126.8	1,505	Negative	....	...	...	...	....	...	
9	26	47.4	0	75.0	127.5	1,495	Negative	0.17	...	...	...	....	...	52.3
10	27	47.3	0	75.0	126.0	1,480	Trace	0.28	...	...	...	....	...	

\* Partial fast day.

TABLE 7.—DIETARY RECORD OF CASE 2414 (THIRD ADMISSION) GROUP 4

Date, 1916	Day of Observation	Body Weight, Kg.	Diet			C. H., Gm.	Dextrose		Blood, per Cent.	Evidence of Acidosis					Blood: CO <sub>2</sub> Com- bined with 100 C.c. Plasma, C.c.	NaHCO <sub>3</sub> by Mouth
			Protein, Gm.	Fat, Gm.	Total Diet, Calories		Urine, Gm.	N/10 NH <sub>3</sub> C.c.		N/10 Acid C.c.	N/10 NH <sub>3</sub> + N/10 Acid C.c.	N/10 NH <sub>3</sub> C.c.	N/10 NH <sub>3</sub> + Kg. Body Weight, C.c.			
Feb. 19	1	44.6		Fast					0.26	Heavy	.....	.....	.....	26.4	30	
20	2	44.9	162.8	19.0	845	20	100	0.44	Heavy	4,160	1,350	5,490	122	24.2	40	
21	3	44.8	94.0	22.8	600	87	87	0.47	Heavy	4,080	1,600	5,680	114	34.3	20	
22	4	44.6	94.0	22.8	600	179	179	0.26	Heavy	3,885	955	4,840	108	36.0	40	
23	5	44.6	94.0	22.8	600	103	103	0.26	Heavy	3,895	992	4,887	108	44.5	40	
24	6	45.0	63.0	15.2	400	68	68	0.30	Heavy	2,860	706	3,566	89	47.2	40	
25	7	46.0	63.0	15.2	400	59	59	0.25	Heavy	2,105	675	2,780	60	53.3	40	
26	8	47.0	63.0	15.2	400	54	54	....	Heavy	.....	.....	.....	38	65.5	40	
27	9	48.4	31.5	7.6	200	48	48	....	Heavy	1,705	148	1,853	41	60.9	25	
28	10	49.0	31.5	7.6	200	29	29	0.27	Heavy	1,900	122	2,022	20	60.2		
29	11	49.8	31.5	7.6	200	36	36	....	Moderate	890	60	950	14	54.0		
Mar. 1	12	48.0	Fast			24	24	0.28	Moderate	620	60	680	9	64.1		
2	13	48.0	Fast			23	23	....	Slight	.....	.....	.....	7	64.4		
3	14	47.4	Fast			Trace	Trace	0.27	Slight	.....	.....	.....	6	64.8		
4	15	47.2	Fast			Negative	Negative	....	Negative	396	32	428	6	61.7		
5	16	47.2	Fast	0.8	65	Trace	Trace	0.29	Negative	350	18	308	7	56.2		
6	17	47.0	3.8	0.8	65	Trace	Trace	0.33	Negative	263	8	271	6	58.3		
7	18	47.2	10	1.1	100	Trace	Trace	0.31	Negative	267	24	281	6			
8	19	46.2	15	6.5	120	Trace	Trace	....	Negative	318	24	332	7			
9	20	46.2	25	10.0	150	Trace	Trace	0.26	Negative	.....	.....	.....	.....			
10	21	46.1	30	11.5	180	Slight	Slight	0.22	Negative	.....	.....	.....	.....			
11	22	46.1	3.3	1.8	60	Trace	Trace	....	Negative	.....	.....	.....	.....			
12	23	45.5	...	14.9	160	Negative	Negative	0.26	Negative	.....	.....	.....	.....			
13	24	44.3	...	22.3	240	Negative	Negative	0.22	Negative	.....	.....	.....	.....			
14	25	44.3	10	3.8	60	Negative	Negative	....	Negative	.....	.....	.....	.....			
15	26	44.4	20	8.6	125	Trace	Trace	....	Negative	.....	.....	.....	.....			
16	27	44.0	30	11.3	180	Trace	Trace	....	Negative	.....	.....	.....	.....			
17	28	44.2	10.3	26.3	300	Trace	Trace	....	Negative	.....	.....	.....	.....			
18	29	44.0	...	Fast	805	Negative	Negative	....	Negative	.....	.....	.....	.....			
19	30	43.0	...	50.0	64.4	Negative	Negative	....	Negative	.....	.....	.....	.....			
20	31	43.0	...	50.0	64.4	Negative	Negative	0.25	Negative	.....	.....	.....	.....			
21	32	43.6	...	50.0	64.4	Negative	Negative	....	Negative	.....	.....	.....	.....			

is demonstrated and must be considered in the future feeding and observation of the patient.

GROUP 1.—Case 2234, patient aged 54 years, diabetic for five years, emaciation and clinical symptoms of moderate severity, but mild in ability to tolerate a sufficient diet for maintenance.

The table shows no tendency to acidosis during the period of preliminary observation (January 25 and 26) or during the fasting period (January 28 to 31). The subsequent carbohydrate tolerance test (February 1 to 16) shows a tolerance of at least 150 gm. of carbohydrate when given in the form of green vegetables alone. At this point the patient refused further hospital treatment, but subsequently he tolerated a maintenance diet of 40 calories per kg. body weight, including 30 gm. carbohydrate and 1.5 gm. protein per kg. body weight (From Jan. 25 to Feb. 16, 1916).

GROUP 2.—Case 2686, patient aged 13 years, diabetic one year, extreme in acid intoxication. The patient was admitted on the verge of coma, being so stuporous that it was impossible to attract his attention by any means. The combining power of the blood for  $\text{CO}_2$  (12.2 volume per cent.) agreed with the clinical picture in indicating extreme acidosis. Therefore, the usual preliminary observation period was omitted. Fasting was immediately instituted, and sodium bicarbonate given by mouth (together with the other therapeutic measures described in the text). Within twenty-four hours the  $\text{CO}_2$  combining power of the plasma had risen to 26.8 volume per cent., and there was a corresponding improvement in the clinical condition of the patient, consciousness having completely returned and signs of coma having disappeared. After five days fast the plasma  $\text{CO}_2$  was nearly normal for a child 13 years of age; the patient was alert and apparently in as good condition as could be expected in a normal child after such a fast. The fast was continued for four days more, however, until the patient became aglycosuric.

The subsequent carbohydrate tolerance test showed a tolerance of 90 gm. of carbohydrate when given in the form of green vegetables alone, and a maintenance diet of 40 calories per kg. body weight including 30 gm. of carbohydrate and 2 gm. of protein per kg. was tolerated without glycosuria or acidosis.

A year and a half after admission word was received that the patient had died in coma following a break in diet. (From February 22 to March 28, 1916.)

GROUP 3.—Case 2480, aged 27. Diabetic four years, severe in carbohydrate intolerance and in a continuous low grade acid intoxication despite dietetic treatment. The summary shows a low grade acidosis during the preliminary observation diet (October 15 and 16) and during the subsequent fasting period (October 17 to 25). During the carbohydrate tolerance test (October 25 to November 6) the plasma bicarbonate barely rose above the minimum normal (53 volume per cent.  $\text{CO}_2$ ), never approaching the average normal (65 volume per cent.), and on the maintenance diet (November 8 to 10) it again fell just below 53. (From October 15 to Nov. 10, 1915.)

GROUP 4.—Case 2414, patient aged 17 years, diabetic one year, was severe in carbohydrate intolerance, and admitted with a dangerous degree of acidosis (plasma  $\text{CO}_2$  26.4 volume per cent.). The patient fasted for seven days before admission, following, he thought, the technic employed in this hospital, which he had experienced on two previous admissions.

The summary shows a case in severe acid intoxication (plasma  $\text{CO}_2$  26.4 volume per cent.) on admission to the hospital, after a fast of seven days at home. The fast was continued for another day under hospital observation. This was followed by a further drop in the plasma  $\text{CO}_2$  of 2.2 volume per cent., which, at this low level, with the onset of hyperpnea and his history of fasting at home, was taken as indication enough to interrupt the fast. The second day in the hospital the patient was put on a diet of lean meat and eggs, constituting 19 calories per kg. body weight. This was accompanied by

sodium bicarbonate by mouth. The following morning the hyperpnea had vanished and the plasma  $\text{CO}_2$  had risen to 34.3 per cent. The diet was gradually cut down during the next ten days and the bicarbonate therapy continued until the patient had a normal plasma  $\text{CO}_2$ . The subsequent fast of five days made the patient aglycosuric and cleared up the ketonuria (Gerhardt reaction).

A carbohydrate tolerance test was given after the fasting period. This was so low (only 30 gm. of carbohydrate when green vegetables alone were given) that a second carbohydrate tolerance test was attempted, as it was thought probable that the severe acidosis present on admission had in some way mitigated against a higher tolerance. The second test confirmed the first.

The maintenance diet was then gradually built up to 1,550 calories (39 calories per kg. body weight), which included 2 gm. of protein per kg. body weight. No carbohydrate was tolerated on mixed diet.

The patient died a year later (March, 1917) in coma. (From February 19 to March 21, 1916.)

Individual diabetics vary greatly, not only in their ability to metabolize food without glycosuria, but also in their tendency to develop acidosis. Fasting decreases this tendency in most patients, but greatly exacerbates it in a minority. It has been found that it is possible to divide diabetic patients into four groups, according to their tendencies to develop acidosis, and that more or less typical treatment is required for the members of each group.

In this paper are described the methods employed at the hospital of the Rockefeller Institute to detect as early as possible the development of acidosis and to prevent its progress and typical examples are given of the procedure and results with patients of each group.

# SINO-ATRIAL HEART BLOCK IN A CHILD

WITH OBSERVATIONS ON THE EFFECTS OF ATROPIN AND VAGUS  
STIMULATION \*

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BALTIMORE

The cardiac arrhythmias of childhood are largely confined to those alterations in rhythm which are governed by the rate of stimulus production in the sino-atrial node. This function is stimulated or depressed by the influence of extracardiac nerves, the vagus and the sympathetic, which in the young are especially active. Of the arrhythmias arising in the sino-atrial node, the simple respiratory arrhythmia which characterizes Mackenzie's "youthful heart" is the most common. There is another type of sinus arrhythmia which is independent of the respiration, but which still has a peculiar phasic character. The cardiac cycles increase progressively in length until the rate is notably retarded, then become shorter until the more rapid rhythm is again established. The rhythm of the sinus node may be interrupted by excitation waves arising at some lower point in the primitive cardiac tissue and retrograde stimulation disturb the fundamental rhythm, or the focus of stimulus production may be shifted within the node from one group of cells to another possessing a different inherent rate of impulse production. The function of pacemaker may also be temporarily assumed by specialized tissues elsewhere in the heart, often in the atrial wall or in the atrioventricular node, which, if possessed of a rapid rate of impulse production, will result in a paroxysmal tachycardia or an atrial flutter.

It is known from experimental and clinical evidence that many of these variations in rhythm may be produced by direct or indirect stimulation of the vagus or of the vagus center. The cardiac response of hypervagotonic individuals to reflex stimulation is characterized by marked changes in the pulse rate. Fear, anger, hunger, deepened respiration, the act of swallowing or defecation are accompanied by transient arrhythmia. Direct stimulation by pressure on the vagus, especially that of the right side, will retard the production of excitation waves at the sinus node in hearts susceptible to vagus influence. The oculocardiac reflex, elicited by pressure over the eyeballs, will also cause a retardation of the pulse rate and a lengthening of the cardiac cycle. Susceptibility to vagal influence is often marked during convalescence from fevers. At such times the response to vagal

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\* From the Pediatric and Medical Clinics of the Johns Hopkins Hospital.

stimulation by a slowing of the pulse and a slight arrhythmia is considered by Mackenzie to be evidence of improvement in myocardial tone. In all these conditions there is a delicate balance between the influences of the sympathetic and the vagus. When this balance is disturbed the rate of impulse production varies from beat to beat and a true sinus arrhythmia exists.

It is customary to classify interferences with impulse conduction according to the locality of the obstruction as determined by the interpretation of the electrocardiographic or polygraphic record. The most common example, that to which the term "heart block" is generally applied, consists of a defect in the mechanism of impulse conduction between the atrium and the ventricle. The excitation wave may, however, be interrupted at any point in its course. If the impulse is blocked in the sino-atrial node, the atrioventricular node or in the bundle of His, where only one path is available, the result is a "dropped beat." In other areas an excitation wave blocked in its normal path will traverse an unusual route, and the electrocardiographic picture gives evidence of the irregular course of such an impulse. Sino-atrial block is due to a structural or functional defect or to some neurogenic influence that effectively blocks an excitation wave within the sinus node or between the node and the atrial musculature. There is, therefore, no evidence of atrial activity, and the whole heart comes to a standstill for a period of one or more cardiac cycles. Measurement of graphic records show that in sino-atrial block a regular rhythm underlies the apparent arrhythmia. This fundamental rhythm is maintained at some focus within the sino-atrial node and is represented by atrial contractions whenever excitation waves are released. Each interruption is, therefore, approximately equal to two or more cardiac cycles of normal duration. Sinus arrhythmia of a respiratory or phasic type may complicate a sinus block and at times still further modify the rhythm.

Both complete and partial sino-atrial block have been produced experimentally in animals. By gradual isolation of the sinus node in dogs and by clamping lower portions of the node, Eyster and Meek<sup>1</sup> have been able to reproduce and demonstrate, under electrocardiographic control, the rhythm which characterizes sino-atrial block in man. That which they secured as a result of these manipulations was a functional block due to artificial structural defects, a condition comparable to that usually found in atrioventricular block. Sino-atrial block is sometimes associated with the administration of digitalis. Ten out of eighteen cases collected by Levine<sup>2</sup> were, at the time of

1. Eyster, J. A. E., and Meek, W. J.: *Arch. Int. Med.* **19**:117 (Jan.) 1917.

2. Levine, S. A.: *Arch. Int. Med.* **17**:153 (Feb.) 1916.

observation, under digitalis. White<sup>3</sup> and Parkinson<sup>4</sup> report cases in which this form of block was present only during the periods of digitalis administration. Cushny<sup>5</sup> has produced a two-to-one sino-atrial block with aconitine. Eyster and Meek<sup>6</sup> and Cohn<sup>7</sup> have shown that the condition will follow the administration of morphin in large doses.

Sino-atrial block is not a common clinical finding. Of 2,000 electrocardiographic records taken in the Johns Hopkins Hospital only four show this type of arrhythmia. The condition has been clinically studied by Levine<sup>2</sup> who collected the fourteen cases reported in the medical literature and added to this series four which have come under his own observation. The youngest patient whose case is reported is one seen by Joachim.<sup>8</sup> The patient was a boy, aged 15, with a previous history of rheumatism, mitral insufficiency and acute pericarditis. The only graphic records obtained were from the radial artery. Wilson,<sup>9</sup> in reviewing the circulatory disturbances of childhood, calls attention to the fact that up to that time (1915) no cases of sino-atrial block in childhood had been reported.

The case here presented is one of sino-atrial heart block occurring in a boy, aged 11 years, a patient from the Harriet Lane Hospital in the service of Dr. John Howland, who has kindly furnished the clinical data for this report.

#### CLINICAL REPORT

H. N., a boy, aged 11, was admitted to the hospital June 26, 1917. He is the younger of two children. The mother is of a nervous temperament. The father had rheumatic fever five years ago.

*Past History.*—During infancy the patient had frequent digestive disturbances. Breast feeding was supplemented from the age of six months by various milk modifications. Dentition began at six months. He walked when one year of age and began to talk at the age of 15 months. He is now in the fourth grade at school.

In early childhood he had measles and chickenpox; no mumps, scarlet fever or chorea. He caught cold easily, and frequently had sore throat with fever. The mother states that when the boy was 2 years old she was told that he had a weak heart. His playing was often interrupted because of shortness of breath.

One month ago he was sick with sore throat, headache, fever and vomiting. There was no eruption. He returned to school but complained of headache and pains in the arms. June 19 prostration was marked. He was feverish and the headache increased. The following day his right hip and left ankle became painful. Since then both ankles have alternately been painful and swollen.

*Present Illness.*—On admission his temperature was 101.6 F., pulse 88, respiration 24. His general appearance was that of a rather delicate child, small for his age, resting comfortably in bed and complaining of pain only

3. White, P. D.: Boston M. & S. J. **175**:233 (Aug. 17) 1916.

4. Parkinson, J.: Heart **6**:335, 1917.

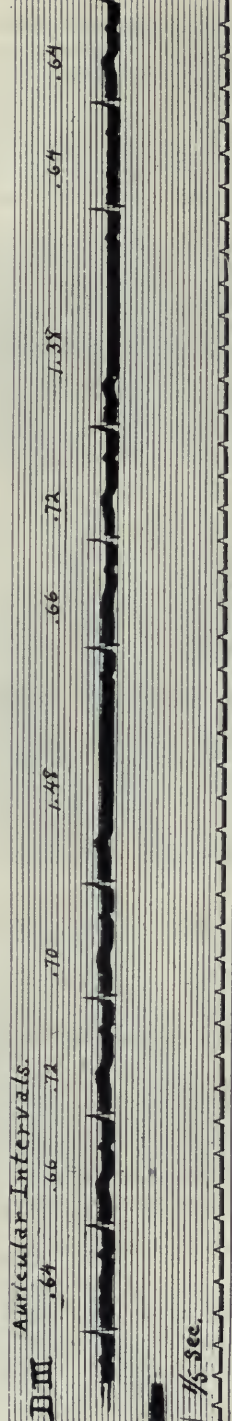
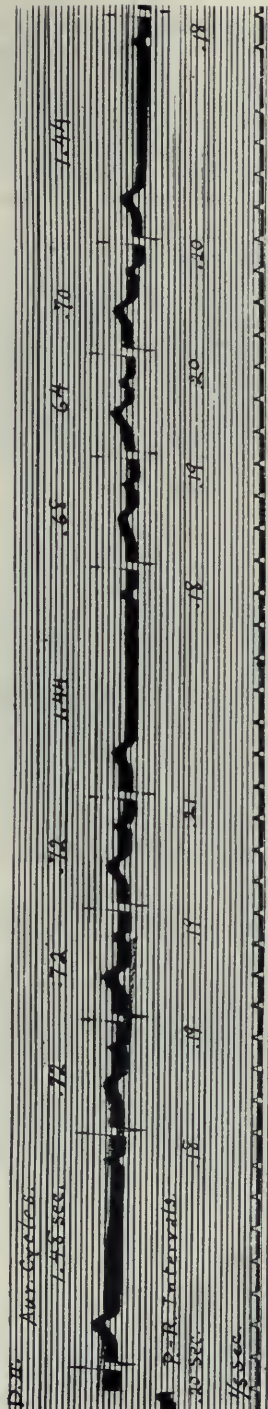
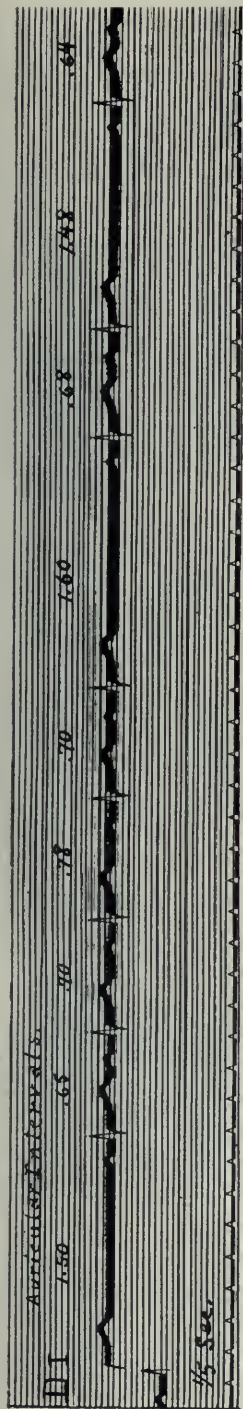
5. Cushny, A. R.: Heart **1**:1, 1910.

6. Eyster, J. A. E., and Meek, W. J.: Heart **5**:137, 1914.

7. Cohn, A. E.: J. Exper. Med. **18**:715, 1913.

8. Joachim, G.: Deutsch. Arch. f. klin. med. **85**:373, 1905.

9. Wilson, F. N.: Am. J. Dis. Child. **10**:376 (Oct.) 1915.



Figs. 1, 2 and 3.—Derivations I, II and III. June 30, 1917. Sino-atrial block. Atrial cycles are measured from P to P. One cm. deflection equals 1 millivolt. Time recorded in fifths of a second.

when moved. He answered questions and cooperated intelligently. On examination the cervical glands were found somewhat enlarged, the inguinal lymph nodes small but palpable. The teeth were in poor condition; there was pyorrhea; the gums bled easily. Both tonsils were markedly enlarged, red and ragged, but without follicular exudate. The lungs were negative. Cardiac dullness was increased to the right. The apical impulse was in the fifth interspace, three and three-fourth inches from the midsternal line. On auscultation the first aortic sound was weak; the second aortic sound was clear, the second pul-

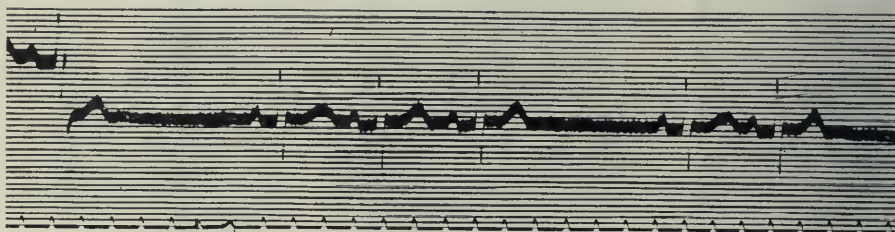


Fig 4.—Derivation II. July 3, 1917. Atropin observation. Control. Sino-atrial block. Ventricular rate 64.

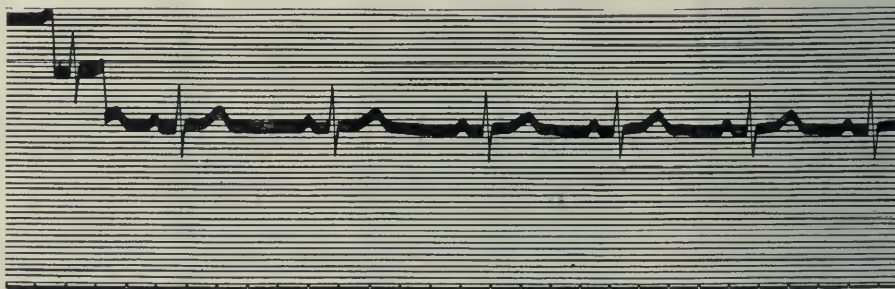


Fig. 5.—Ten minutes after hypodermic administration of  $\frac{1}{150}$  grain of atropin. No block. Slight sinus arrhythmia. Rate 68.

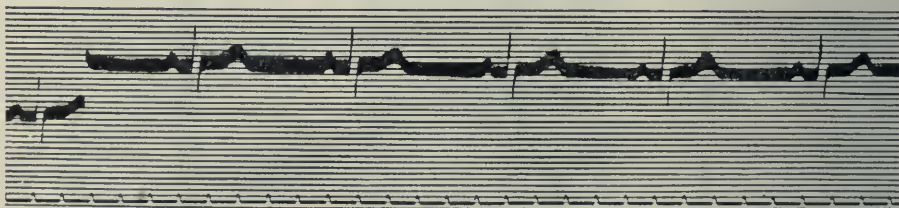


Fig. 6.—Twenty-three minutes after atropin. No block. Regular rhythm. Rate 58.

monic sound was rough and accentuated. A soft, blowing murmur was heard over the precordium but was only faintly transmitted beyond the apex. Occasional "dropped beats" were noted. The liver was not enlarged; the spleen was not palpable. There was slight tenderness in the region of the left shoulder; the left ankle was swollen, reddened and tender. Other joints were negative. Reflexes normal. The urine showed albumin in small quantities but there were no pus cells, casts or red blood cells, no sugar and no acetone. The von Pirquet reaction was negative. The white blood count was 18,400.

On admission sodium salicylate and sodium bicarbonate were prescribed in suitable doses. No digitalis was administered.

*Clinical Course.*—June 27, 1917: Pain in ankle subsided. Patient's condition improved; no change in heart findings. Temperature 100 F.

June 30: An electrocardiographic examination was made.

July 2: Cardiac dullness extends only three inches from the midsternal line. The systolic murmur is the same. The second pulmonic sound is sometimes reduplicated. Temperature 99 F.; pulse during sleep is 50 and fairly regular.

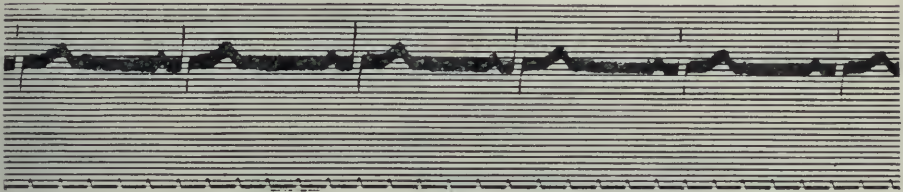


Fig. 7.—Thirty minutes after atropin. No block. Regular rhythm. Rate 55.

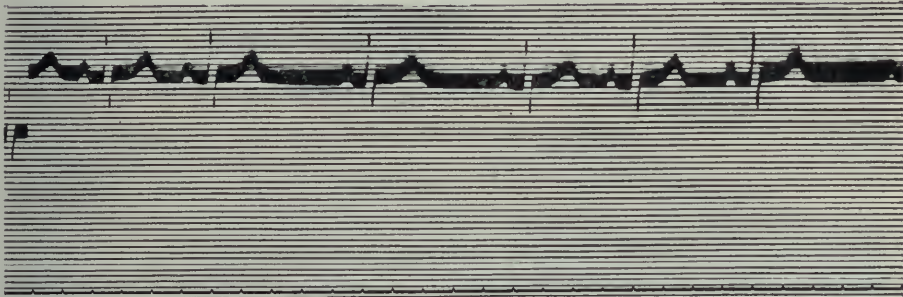


Fig. 8.—Forty-three minutes after atropin. Sinus arrhythmia. Rate 68.

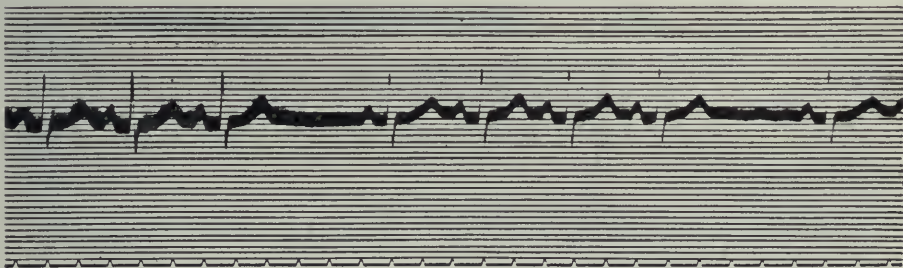


Fig. 9.—Fifty-five minutes after atropin. Sino-atrial block returns.

July 3: An electrocardiographic examination was made. Atropin, 1/150 grain, was administered.

July 4: The patient had gastrointestinal disturbances, and his pulse was very irregular.

July 5: The pulse was irregular, with pauses of different lengths. The rate was about 48.

July 9: An electrocardiographic examination was made and atropin, 1/100 grain, was administered.

July 11: An electrocardiographic examination was made.

July 13: Final note. The general condition of the patient was good. The apical impulse was two and three-fourths inches from the midsternal line. The pulse was irregular, about 60 per minute. The temperature was normal. The patient was discharged improved.

Feb. 15, 1918: The patient returned for examination. He has been attending school. His general health was good. There was no recurrence of any pains, but there was slight shortness of breath on exertion. The apical impulse was well within the mammary line. The systolic murmur at the apex was not transmitted to the axilla. The pulse showed the same type of arrhythmia as on previous examinations. An electrocardiographic examination was made. Atropin, 1/75 grain, was administered.

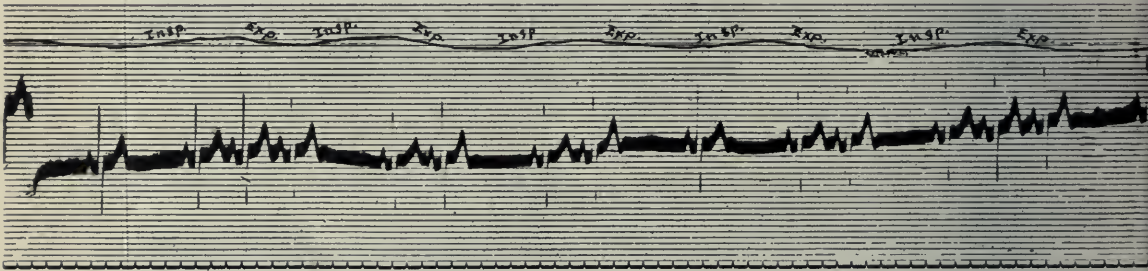


Fig. 10.—Derivation II. July 9, 1917. Control with respiratory curve. Sino-atrial block. Slow film.

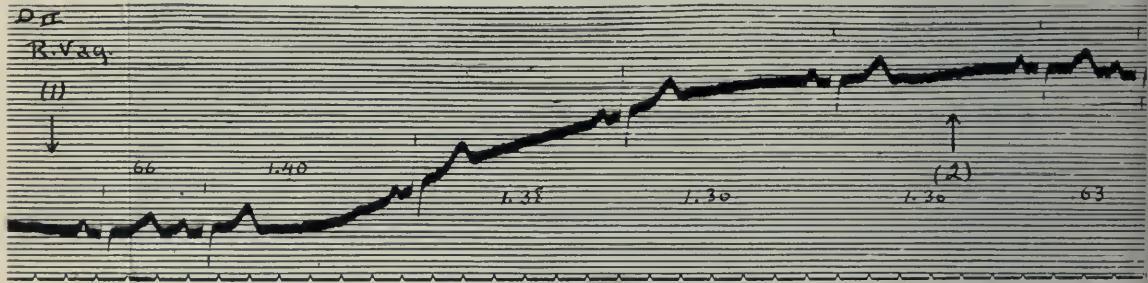


Fig. 11.—Before atropin. Pressure on right vagus. Applied at (1), released at (2). Block is increased.

#### ELECTROCARDIOGRAPHIC STUDY

June 30, 1917.—The principal waves of the electrocardiogram (Figs. 1, 2 and 3) are normal for a child of this age. The R waves are low in all three leads; the S deflection is prominent in the first and second leads. P waves are normal. T is upright in all leads. The sequence is normal. Conduction time is slightly prolonged and measures from 0.18 to 0.21 second. Arrhythmia of an unusual type is present in which the normal rhythm is interrupted by frequent pauses approximately equal to two normal cycles. There is no evidence of auricular activity during these intermissions. The P-R interval is slightly longer in the cycles just preceding the pause. Measurement of the individual atrial cycles (P-P) shows that the atrial intervals preceding the intermissions are usually longer than those which immediately follow them. The long cycles are either equal to, or slightly longer than, the period occupied by two short cycles. The short atrial cycles which represent the fundamental sinus rhythm measure

on the average 0.67 second, indicating a production rate of 90 or 92 excitation waves per minute. The long pauses average 1.45 seconds. The diagnosis is sino-atrial block.

July 3, 1917. Controls were taken which showed (Fig. 4) the same arrhythmia as on June 30. There are frequent pauses equal to two or four normal beats. The average length of the normal cycle is 0.65 second; the average length of the pause is 1.4 seconds. The fundamental rate of sinus is 92. The ventricular rate is 64. Atropin,  $\frac{1}{150}$  grain, was given hypodermically.

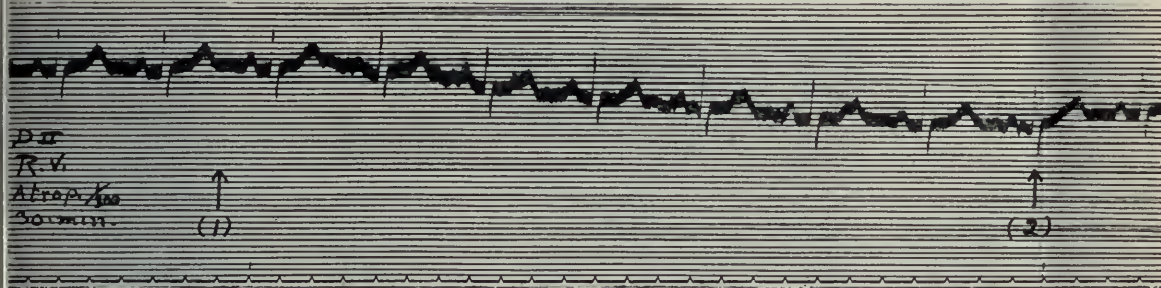


Fig. 12.—Before atropin. Pressure on left vagus. Applied at (1), released at (2). No appreciable effect on rhythm.

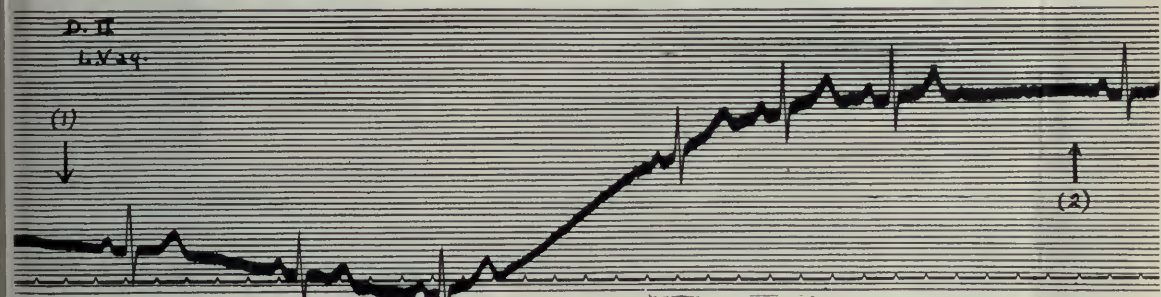


Fig. 13.—Before atropin. Oculocardiac reflex. Pressure applied at (1), released at (2). Block is increased.

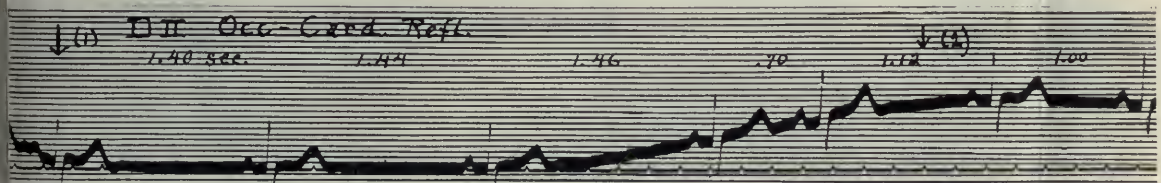


Fig. 14.—After atropin. Pressure on right vagus. Applied at (1), released at (2). No change in rhythm.

Ten minutes after atropin was given the sinus block disappeared (Fig. 5), but a slight sinus arrhythmia persisted. The cardiac cycles measured from 0.70 to 0.98 second. The rate was 68; the P-R interval was 0.18 second.

Twenty-three minutes after atropin was given the rhythm (Fig. 6) was regular; the rate was 58; the cardiac cycles measured 1.02 to 1.08 seconds; the P-R interval was 0.18 second.

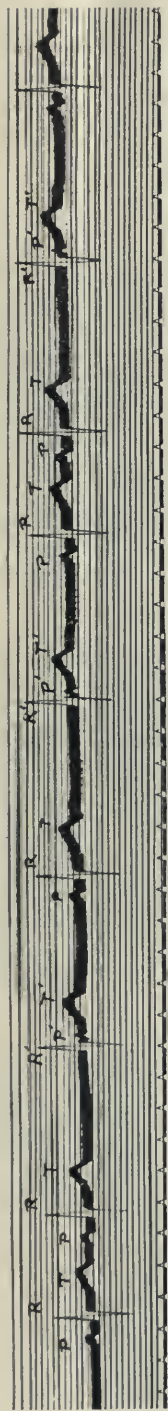


Fig. 15.—Derivation II. July 11, 1917. Sino-atrial block. During the long three-cycle intermissions nodal extra-systoles appear (R'P'T').

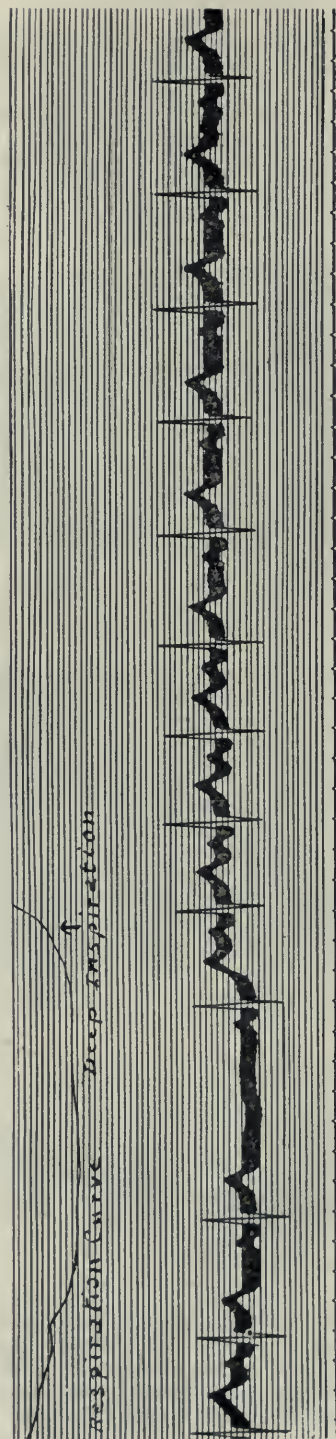


Fig. 16.—Derivation II. Feb. 15, 1918. Sinus block disappears while breath is held in full inspiration. Sinus rate is retarded.

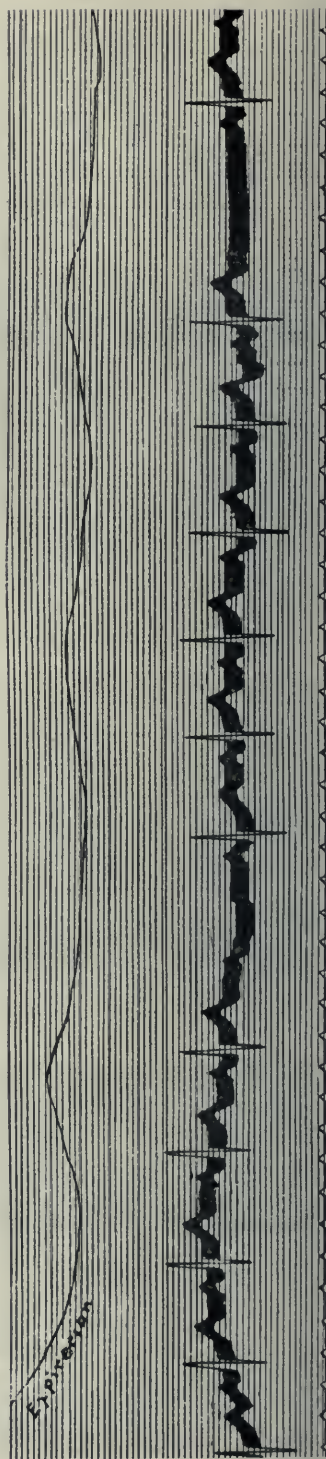


Fig. 17.—Continuation of record shown in Fig. 16. There is an intermission of twelve seconds between Figs. 16 and 17. On expiration the characteristic sinus block returns.

Thirty minutes after atropin was given the rhythm was regular (Fig. 7); the rate was 55; the cardiac cycles measured 1.08 seconds; the P-R interval was 0.17 second.

Forty-three minutes after atropin was given there was (Fig. 8) slight sinus arrhythmia; the rate was 68; the cardiac cycles measured 0.71 to 1.06 seconds.

Fifty-five minutes after atropin was given the sino-atrial block (Fig. 9) had returned. There were pauses after three to six normal cycles. The short cycles measured 0.56 to 0.60 second; the pauses measured 1.12 to 1.24 seconds.

July 9, 1917. Controls show sinus block as before (Fig. 10). The short cycles measure 0.60 to 0.66 second; the pauses measure 1.32 to 1.40 seconds. The ventricular rate is 60. The P-R interval is from 0.17 to 0.19 second. A respiratory curve taken with the electrocardiogram shows the relation of the respiration to the arrhythmia. The long pauses occur usually, but not always, during the inspiratory phase. On holding the breath the block entirely disappears, the rate is 57 per minute. Pressure on the right vagus increases the block and eliminates the short cycles; four blocks occur in succession. Pressure on the left vagus produces no appreciable change (Fig. 11). Firm ocular pressure definitely increases the number of blocked impulses (Fig. 12). Atropin,  $\frac{1}{100}$  grain, was given hypodermically. Ten minutes afterward there was no block. Sinus arrhythmia was present with cycles measuring from 0.63 to 1.15 seconds; the ventricular rate was 66. Sixteen minutes after the injection of the atropin the rhythm was regular. Twenty-two minutes after the injection the rhythm was regular, the rate was 73 and the cardiac cycles measured from 0.72 to 0.88 second.

Twenty-six minutes after atropin injection the rate was 82. Pressure at this time on the right vagus produced no effect (Fig. 13). Deep pressure on the eyeballs produced a brief return of the sinus block showing that the vagus was still partially active. Sixty minutes after atropin was given the sinus block type of arrhythmia returned; the fundamental rhythm became more rapid; the short cycles measured from 0.56 to 0.60 second; the pauses measured from 1.08 to 1.14 seconds; the ventricular rate was 68.

July 11, 1917. A sino-atrial block was present, but electrocardiograms also showed frequent nodal extrasystoles (Fig. 14). The short cycles measure 0.64 to 0.68 second. After one or two normal beats there is an interval of from 2.22 to 2.30 seconds before another normal excitation wave appears. This interval is greater than those previously found and is approximately equal to the period occupied by three normal cycles. In the middle of this interval there appears, each time, a nodal extrasystole. The atrium and ventricle contract simultaneously; a small diphasic P wave appears between the R and the T, following the R wave by 0.08 second. The extrasystole is always the same distance, 1.12 to 1.16 seconds from the preceding R wave. The ventricular rate is 58. Holding the breath in full inspiration eliminates the extrasystoles and the arrhythmia. While the breath is held the cardiac cycles measure from 0.78 to 0.86 second with a ventricular rate of 80.

Feb. 15, 1918. Electrocardiograms show sino-atrial block of the same type as existed in July, 1917. The short cycles are somewhat more numerous. No extrasystoles were found. Right vagus and ocular pressure, as on former occasions, produced an increase in the number of dropper beats. The arrhythmia again disappeared when the breath was held in full inspiration (Figs. 15 and 16). Atropin,  $\frac{1}{15}$  grain, was given hypodermically. Five minutes later the arrhythmia was still present. In ten minutes it had disappeared; the rate was 80. Twenty minutes after atropin administration the rate had increased to 115. One hour later it was 120, the rhythm still being regular. Two hours after the atropin injection the heart had resumed its characteristic arrhythmia.

#### DISCUSSION

The arrhythmia found in this case is that usually referred to as "sino-auricular block." There is a complete standstill of the entire

heart for one or more beats, the intermissions being separated by one to six normal cardiac cycles. The blocks which characterize the records from this patient may hypothetically result from a failure of the sino-atrial node to generate an excitation wave, from a failure of the atrial musculature to respond to the excitation or from interference with the impulse in its passage to the atrium. The persistence of a fundamental rhythm underlying this arrhythmia is evidence of the maintenance of rhythmic impulse production. There is no evidence of diminished atrial excitability and the atrium responds to every excitation wave when the rate is much augmented.

The arrhythmia is best explained by the existence of some factor which interferes with the transmission of correctly timed excitation waves. Such a functional defect may be dependent either on structural changes or the influence of depressor nerves. The sino-atrial block produced experimentally by Eyster and Meek<sup>1</sup> is essentially a functional block due to structural changes. Our records from this case present some of the same characteristics. After several normal contractions an impulse fails to pass. In the series of normal beats the atrial cycles preceding an intermission are slightly longer than those which follow it, suggesting an increasing delay in impulse transmission prior to the appearance of the block. Such an observation was used by Levine<sup>2</sup> as a basis for the hypothesis that sinus arrhythmias associated with sino-atrial block are due to a progressive delay in impulse transmission. Were this hypothesis applicable in the explanation of this arrhythmia, a retardation in the rate of impulse production would eliminate, and an acceleration would increase, the block. The rate was reduced and the block eliminated in this case by holding the breath after deep inspiration, but when stronger vagus stimulation was employed, directly by pressure on the right vagus, or indirectly by ocular pressure, the intermissions increased in frequency. The administration of  $\frac{1}{75}$  grain of atropin increased the rate to 120 per minute, but with the acceleration the blocks disappeared. It is evident that if there be in this case any structural defect, it is a minor factor, and that the abnormal rhythm is due chiefly to vagus influence. The electrocardiograms taken on July 11 (Fig. 14) in which there occur three cycle pauses broken by a nodal extrasystole, bear a striking resemblance to those taken by Cohn<sup>7</sup> after the administration of morphin to "right vagus dogs," those in which the left vagus had been severed.

It is known that structures in various parts of the heart have the power, under certain conditions, of initiating excitation waves, and that these areas have different rates of impulse production. Meek and Eyster<sup>10</sup> have shown that even within the sino-atrial node the

10. Meek, W. J., and Eyster, J. A. E.: *Am. J. Physiol.* **34**:368, 1914.

location of the pacemaker may be changed by moderate vagus stimulation. It is possible that different portions of the node have different rates of stimulus production, and that by a shifting of the pacemaker within the node the rhythm is changed. Macleod<sup>11</sup> suggests that varying degrees of vagus stimulation may have a selective action on the strength, rate, impulse transmission and excitability of the heart muscle. Varying the degree of vagus paralysis in a hypervagotonic individual would inversely modify the strength of vagal stimulation.

The primary action of atropin is to stimulate the vagus center in common with other medullary centers. A preliminary slowing of the pulse is sometimes observed, but this is quickly replaced by the tachycardia which accompanies the atropin action on the vagus endings. To modify the action of the vagus, atropin was given hypodermically. A small dose,  $\frac{1}{150}$  grain, produced a slowing of the pulse and an elimination of the arrhythmia. This effect appeared in ten minutes and persisted for almost an hour without the acceleration which usually follows atropin administration. On another occasion the same result followed the injection of  $\frac{1}{100}$  grain of atropin. The arrhythmia disappeared and a regular rhythm, slower than the fundamental rhythm, was maintained for an hour. The administration of  $\frac{1}{75}$  grain produced a rapid increase in the rate of the heart to thirty beats above the fundamental rhythm. The arrhythmia was eliminated. The larger dose produced a simple tachycardia, the usual result of atropin administration. Wilson<sup>12</sup> concludes, from observations on patients in whom he produces a temporary atrioventricular rhythm, that there is a selective action of atropin by which the vagus terminations in the atrioventricular node are affected before those in the sinus node. In a similar manner it appears that in the instance here recorded atropin acts first on the vagus terminations in and about the sinus node which control conductivity and later on those which control the rate of impulse production.

A prominent feature of these electrocardiograms is the persistence under normal conditions of a fundamental sinus rhythm. The portion of the sinus node which acts as pacemaker has, it is evident, a rate of stimulus production which results in the formation of excitation waves at the rate of 90 per minute. This has been referred to as the fundamental rhythm. The demands of the circulation only call for 58 to 66 ventricular contractions per minute. The adjustment of the sinus rate to the circulatory demand is largely dependent upon the balance established between the opposing influences of the vagus and the sympathetic nerves. While occasionally this heart shows beats of intermediate

11. Macleod, J. J.: *Physiology and Biochemistry in Modern Medicine*, 1918, p. 227.

12. Wilson, F. N.: *Arch. Int. Med.* **16**:989 (Dec.) 1915.

length, nearly all cardiac cycles fall into two groups; those which measure approximately 0.66 seconds, a rate of 90 per minute, and those which occupy 1.20 to 1.40 seconds. The pacemaker is adjusted to the 90 per minute rate, and the vagus, instead of depressing stimulus production and thereby reducing the rate, affects first the conductivity and produces a sufficient number of intermissions to bring the rate to about 60 contractions per minute, the number required to properly maintain the circulation. In Figure 14 is shown a block of three cycles. This delay permits a ventricular release, the excitation wave originating in or near the atrioventricular node and resulting in the simultaneous contraction of auricles and ventricles. By means of this nodal extrasystole introduced in each three cycle intermission, the heart maintains the requisite number of contractions per minute.

The action of small doses of atropin in eliminating the arrhythmia without producing sufficient vagal inhibition to permit the acceleration of impulse production, and the persistence of this slow, regular rhythm are of clinical interest. They indicate a prolonged primary atropin effect which moderately stimulates the vagus center and retards impulse production, while coincident with this is a selective peripheral action of atropin on the vagus endings which control impulse transmission, thus facilitating the passage of excitation waves to the atrium.

#### SUMMARY

A case is reported of a child, 11 years old, with acute arthritis, who presents a typical sino-atrial block. Changes in heart rate and rhythm by vagus stimulation and by the administration of atropin are demonstrated. It is found that atropin in small doses will eliminate the arrhythmia without producing an acceleration of the heart rate. Electrocardiographic records accompany the report and illustrate the observations.

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## FACTORS DETERMINING THE RELATIVE INTENSITY OF THE HEART SOUNDS IN DIFFERENT AUSCULTATION AREAS

AN EXPERIMENTAL STUDY \*

CARL J. WIGGERS, M.D.  
CLEVELAND

### I. INTRODUCTION

It is commonly accepted as a fact that the absolute and relative intensities of the two heart sounds not only offer valuable information concerning the dynamic state of the heart muscle, but also serve as a criterion of the pressure conditions in the greater and lesser circuits. This conception, based on plausible physical assumptions and fortified by clinical experience, has, however, received only cursory attention from experimental investigators.

Lewis,<sup>1</sup> in his experimental studies of the recorded heart sounds, tested the effect of raising the arterial pressure by aortic compression, but was unable to corroborate one general idea, viz., that high arterial pressure, per se, is responsible for an accentuation of the aortic second sound. On the other hand, the experiments of Dean and myself<sup>2</sup> indicated that the intensity of the sounds directly recorded from the heart is determined by the dynamic conditions of the circulation. Thus, we found that the vibrations comprising both the first and second sounds increased, not only in amplitude, but also in number of vibrations, when the ventricles increased in vigor and the blood pressure was simultaneously elevated either by the injection of epinephrin, by aortic compression or by asphyxia. These experiments did not determine, of course, whether the increased ventricular activity or the simultaneous increase in arterial pressure was fundamentally responsible for the accentuated sounds; nor was the question of changes in the relative intensity of sounds over different cardiac areas investigated. With such questions, this investigation is concerned.

\* From the Physiology Laboratory of Western Reserve University, School of Medicine, Cleveland.

1. Lewis: *Quart. J. Med.* 4:241, 1913.

2. Wiggers, C. J., and Dean, Jr., A. L.: *Am. J. Physiol.* 42:476 (Feb.) 1917.

## II. METHODS OF INVESTIGATION AND APPARATUS

It is possible, by experimental methods, to modify the circulation so that changes in blood pressure are directly due to or occur independent of cardiac activity; it is possible, also, to modify the circulation so that the pressures in the pulmonary and systemic circuits alter in reverse directions. When such changes are produced within short intervals of time, the changes in intensity of sounds over different cardiac areas can be determined by stethoscopic auscultation or recorded by instrumental means.

To accomplish the latter end, two or three receivers, one each over the apex region, the pulmonary area and the aortic area were snugly applied by an elastic band to the shaved thorax of a dog and held in close apposition by anointing the spot with petrolatum. The sound vibrations were then transmitted by rubber tubing to the sound recording capsules described by Dean and myself,<sup>3</sup> or, in some cases, where a third sound was also recorded, to a microphone connected through an induction coil with a string galvanometer. In all of these experiments, the technical procedures carefully explained in my previous communications with Dean<sup>3</sup> were followed.

## III. CRITERIA FOR DETERMINING VARIATIONS IN INTENSITY OF RECORDED HEART SOUNDS

The intensity of tones appreciated by the human ear is directly proportional to the force imparted to the tympanum and is therefore dependent upon the amplitude of vibrations, not only, but upon their frequency as well, factors which may be expressed by the formula  $I_a = (NA)^2$ . It has, therefore, been proposed by Einthoven<sup>4</sup> that the relative intensity of the heart sounds may be computed according to this formula from photographic records and expressed numerically. This was at first attempted in connection with this investigation, but later given up as unfeasible on the following grounds:

1. The heart sounds, as shown most clearly in Einthoven's laboratory by Battaerd,<sup>5</sup> are composed of vibrations which are exceedingly irregular, both as regards their amplitude and period so that no average amplitude or period can be assigned to the sounds.

2. Owing to a loss of energy in transmission of sound waves to the chest wall, the vibrations originating within the heart reach the thoracic wall much reduced in their amplitude. Of these, a variable number have a vibration frequency which is subminimal, in the sense that they

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3. Wiggers, C. J., and Dean, Jr., A. L.: *Am. J. M. Sc.* **153**:666 (May) 1917; also *Arch. Int. Med.* **22**:28, 1918.

4. Einthoven: *Arch. f. d. gesam. Physiol.* **120**:31, 1907.

5. Battaerd: *Heart* **6**:121, 1915.

do not affect the recording membrane at all. When the amplitude of all vibrations increases, the graphically recorded vibrations become greater in number and, consequently, waves with still different vibration periods are added to the sound complexes. If these are considered, the average frequency of the vibrations—composing particularly the first sound—changes in such a way that the suggested computation has no correct relative value in estimating the objective intensity of a sound.

A rougher, but nevertheless a better estimate of the intensity of the sounds and one which more nearly agrees with the auscultatory findings, can be made by comparing the general picture presented by the vibration groups composing each sound. Thus, if the intensity of the sound increases, the amplitude of the whole wave group increases and the total number of vibrations which enter into the sound component becomes greater. If, on the contrary, the intensity of a sound is reduced, not only is the general amplitude of the sound vibrations much smaller, but the number of vibrations entering into its complex is reduced. This, of course, necessitates that a control record of the sounds be taken previous to the time that the circulation is modified by experimental procedures. Inasmuch as the heart sounds of the dog vary greatly in their intensity with the phases of respiration, it is furthermore necessary to make all comparisons during the same respiratory phase. Since the respirations alter their rate and depth, however, during the experimental procedures employed, it is necessary to make all comparisons during the time of expiratory rest.

#### IV. EXPERIMENTAL PROCEDURE

Animals which were kept evenly anesthetized by morphin and chloretone were placed on their backs. In the earlier experiments records of the vibrations from the right and left second interspaces and from the apex region were simultaneously taken. Inasmuch as it was found, however, that the directional variation of the first and second sound corresponded in the apex region and over the right second interspace, the experiments were simplified by taking only records from the pulmonic and apex regions in the later experiments. In order to preclude possible instrumental irregularities, the additional precaution was taken in the earlier experiments of connecting each area, in turn, with every sound recording capsule used in registration.

As soon as possible after a control of the normal sounds had been recorded, nerves were stimulated or drugs injected, the resulting effect being controlled in a rough manner by a continuous record of the mean carotid pressure recorded on a revolving kymograph. At sufficient intervals, i. e., usually during the onset of an effect, during

its maximum action, during its decline and after normal conditions had been restored, the sound vibrations were again recorded on the photokymograph. The time that these photographic sound records was taken was also indicated underneath the blood pressure on the kymograph through an automatic electrical signal arrangement.

#### V. EXPERIMENTAL RESULTS AND DISCUSSION

The results now to be analyzed were found to agree in all the separate trials carried out on fourteen different dogs.

1. *The Influence of Heart Rate Changes on the Intensity of the Heart Sounds.*—Inasmuch as many experimental procedures are attended by a change in heart rate, and inasmuch as the rate of the heart varies considerably in auscultated subjects, it was first necessary

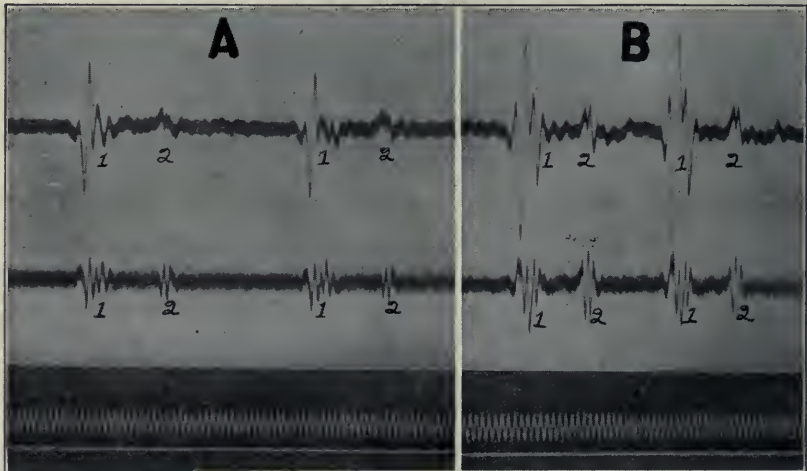


Fig. 1.—(Two-thirds actual size.) Two segments of records showing the change in amplitude of recorded sounds during cardiac slowing, A, during vagus slowing and B, after return to normal rate. Upper record, apex sounds; middle record, pulmonic sounds; lower record, time in 0.02 sec.—1, 2, first and second sound complexes (Experiment C, 210, V).

to study the effect that such primary changes in rhythm produce in the intensity of the heart sounds recorded from different thoracic areas.

In these experiments slowing was induced by mild stimulation of the peripheral end of the vagus nerve; acceleration, either by vagus section or by stimulation of the accelerator nerves.

(a) *The effect of cardiac slowing produced by moderate stimulation of the peripheral end of the vagus nerve.*—The typical effects of mildly stimulating the peripheral end of the vagus nerve are illustrated in the two segments shown in Figure 1. As indicated by the

amplitude and number of vibrations, the intensity both of the first and second sound decreases appreciably over both the pulmonary area and the apex when the heart rate slows.

(b) *The effects of cardiac acceleration produced by vagus section or accelerator stimulation.*—Cardiac acceleration appears to have a variable effect on the intensity of the heart sounds. The first sound is chiefly affected. At times no alteration is apparent, at times, again, an increased amplitude is observed or even a slight decrease may result. Even if allowances are made for the possible shifting of position of the receiving tambours, the results in any given experiment cannot readily be accounted for on experimental grounds.

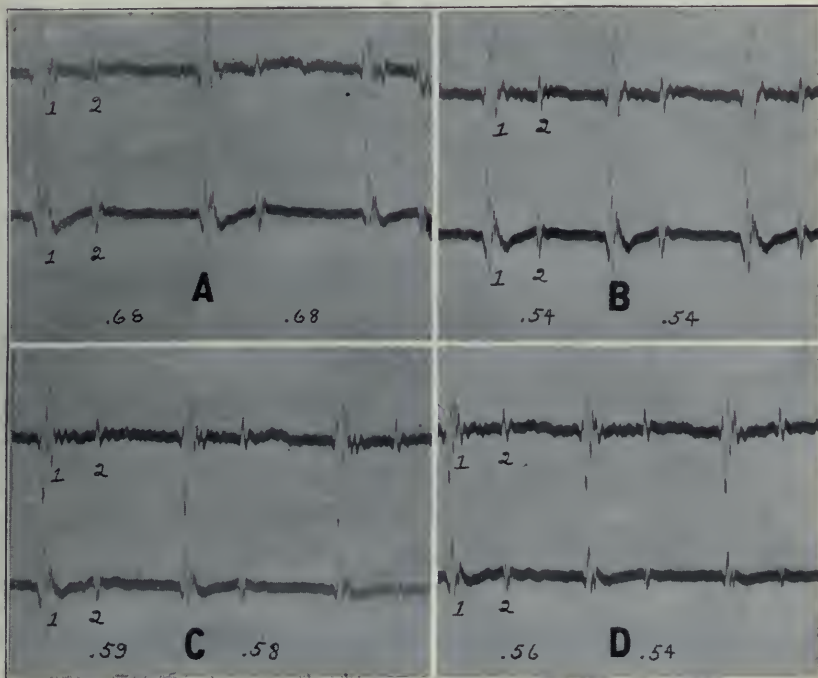


Fig. 2.—(One-half actual size.) Four segments of heart sound records showing effect of cardiac acceleration. Upper record, apex sounds; lower record, pulmonic sounds. Figures .68, .54, etc., marked on curve give duration of heart cycles. Detailed description in text. (Experiment C, 207, III).

In Figure 2, four segments from such an experiment are shown. The first segment, A, is a normal control. The segment, B, shows the sounds after acceleration was produced by section of both vagus nerves. Both sounds at the apex as well as over the pulmonic area are accentuated, as shown both by the larger amplitude and number of vibrations. At the time that the record, C, was taken, the heart had slowed to a slight extent. The first sound is reduced in amplitude in

both curves, the second sound, especially in the pulmonic tracing. Record D was taken during further acceleration of the heart induced by stimulation of the stellate ganglion. All sounds are somewhat reduced over both the apex and pulmonic area.

(c) *Discussion of Results.*—It is common knowledge that when the vagus nerve is stimulated and the ventricles are thus slowed, a fall of the mean systemic and pulmonary arterial pressure results, due to a decrease in the minute volume discharged by the heart. The experiment shows that this fall of pressure, even if moderate, is accompanied by a slight enfeeblement of the second sound; whereas, if the

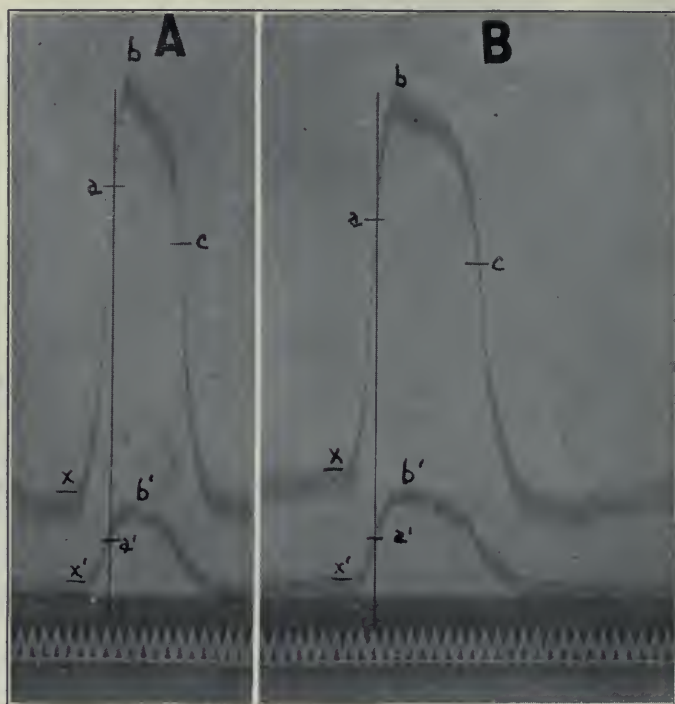


Fig. 3.—(One-half actual size.) Two segments of records showing, left (upper) and right (middle) intraventricular pressure curves. A, normal curves; B, during vagal slowing. Lower curve, tuning fork—50 v.d. Detailed analysis in text. (Experiment C, 216).

pressure drops to any extent, the sounds, both first and second, are diminished in all regions.

Myocardiographic tracings of the ventricles indicate that during vagus stimulation the individual beats are more vigorous and volume curves of both ventricles indicate that the aggregate systolic discharge of the two ventricles increases. We are thus confronted with the

fact that the stronger ventricular beats are accompanied by first sounds of diminished intensity, and we might infer therefrom that the intensity of the first sound is no index of ventricular efficiency.

This unexpected and apparently paradoxical relation led me to reinvestigate the effects of vagal slowing on the right and left intraventricular pressure curves. From such records, it appears that the dynamic effects of continued vagal stimulation are not alike in the right and left ventricles, a fact to which attention has heretofore apparently never been attracted. In Figure 3 are shown two segments of the right and left intraventricular pressures before and during vagus stimulation. The normal pressure curves in the two ventricles may first be considered (A). Owing to the fact that the a-v valves close early in systole, and that the semilunar valves remain closed for an additional short period, each ventricle during its early phase of systole is not able to decrease in volume nor to shorten its fibers; hence the energy of contraction is utilized to develop intraventricular tension. This mode of contraction is spoken of as isometric and consequently

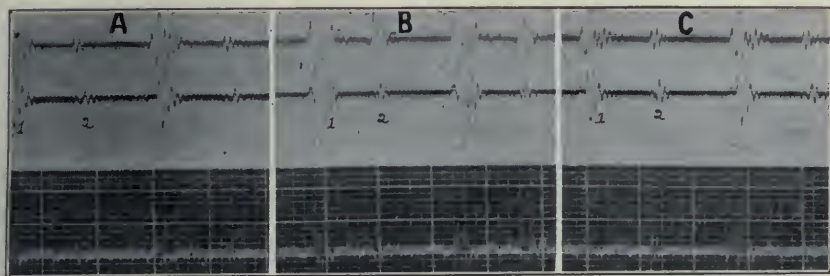


Fig. 4.—(Two-fifths actual size.) Three segments of sound records showing the amplitude of sounds. A, before; B, during central vagus stimulation; C, after return of arterial pressure to normal. Upper record, apex sounds; middle record, pulmonary sounds; lower record (taken by Einthoven's phonocardiographic method), aortic sounds. Abscissae = 0.04 sec. (Experiment C 143, IV).

the interval elapsing before blood is expelled is aptly and concisely referred to as the *isometric period* of systole. This interval extends to the point marked *a* in Figure 3. It is quite obvious upon reflection that the height to which the isometric pressure rises (point *a*) is determined by the height of the aortic pressure at this time, i. e., the higher the aortic pressure at the beginning of systole, the higher the isometric pressure becomes.

If we compare the right and left intraventricular pressure curves before and during vagus slowing, it is evident that, in the case of the right heart the height of isometric pressure, *a'*, is not greatly altered, while the maximum pressure developed during ejection, *b'*, is dis-

tinctly higher. In the left ventricle, on the other hand, such an effect is very transient, lasting for only one or two beats. After this, as shown in segment B of Figure 3, the height of the isometric pressure, *a*, decreases greatly owing to a falling arterial pressure. The maximum pressure reached during ejection, *b*, is also necessarily somewhat lower. Thus we have a reduction of pressure developed within the left ventricle at the same time that the systolic discharge is distinctly increased.

*The reduction in the intensity of the first sounds makes it apparent that the loudness of the first sound is related, not so much to the efficiency of the ventricle as a pumping mechanism as it is to the intra-cardiac tension developed; and especially to the tension developed before the semilunar valves open.* This accords entirely with the observations previously made by Dean and myself,<sup>2</sup> viz., that the vibrations of the first sound reach their maximum intensity before the ejection period has begun, i. e., during the isometric interval.

Cardiac acceleration produced either through double vagotomy or by stimulation of the accelerator nerve, should produce precisely

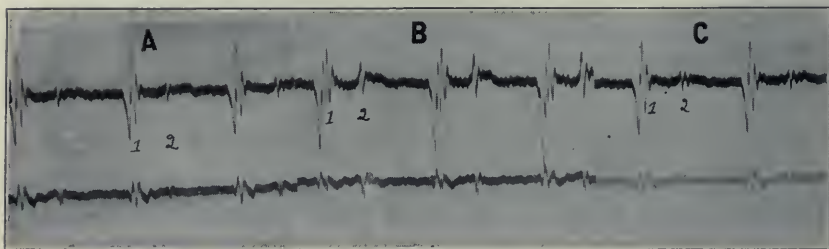


Fig. 5.—(Two-fifths actual size.) Three segments of records showing the amplitude of sounds. A, before; B, during aortic compression; C, after release. Upper curve, apex sounds; lower curve, pulmonic sounds. (C 207, XIII.)

the opposite effect. This result, as shown in the record B of Figure 2, was generally found to be the case. It also harmonizes with the general clinical observation that the first sound is louder in individuals with rapid heart rates. Experimentally, there are, however, distinct exceptions, as shown specifically in the segments C and D of this figure. The cause of this is easily explained. A careful comparison of heart sound records with the simultaneously recorded blood pressure tracings shows without exception that whenever acceleration produces a fair elevation of arterial pressure and an increase in the height of isometric pressure, then the first aortic and apex sounds are also increased. Whenever, through compensatory mechanisms, e. g., reflex dilation, no distinct elevation of arterial pressure occurs and the isometric pressure does not rise above normal, then the first sounds do not alter, or, as is shown in this record, they may even

decrease slightly. These observations establish the fact that changes in heart rate can affect the intensity of the heart sounds only through the attendant dynamic disturbances incurred thereby.

Inasmuch as changes in heart rate are themselves capable of modifying the intensity of the heart sounds, it is obviously necessary to eliminate them, or, at least to take them into consideration in order to evaluate the effect that other circulatory conditions have on the intensity of the sounds. Where heart rate changes occur secondarily through nervous reflexes it is quite possible to eliminate them through the severance of the vagus nerves or paralysis of their terminals by atropin. Certain procedures, however, modify the heart rate through a direct action which cannot be prevented. The foregoing results, viz., that changes in intensity accompanying changes of heart rate are not determined by changes in rate per se, but secondarily by pressure changes induced, are of fundamental help in such instances.

2. *The influence of changes in the total arterial resistance in the intensity of the heart sounds.*—If, as seems probable from previ-

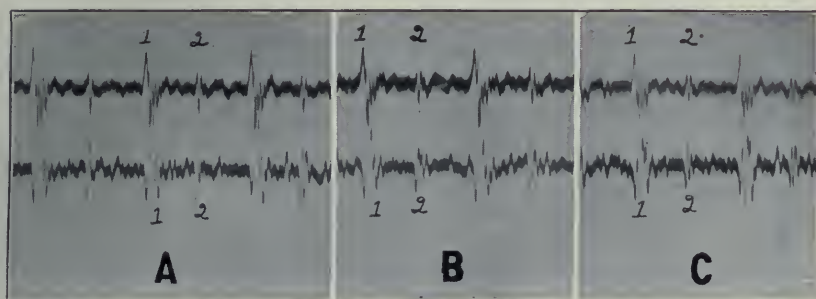


Fig. 6.—(One-half actual size.) Three segments of records showing the relative amplitude of sounds. A, before; B and C, during two stages of pressure decline following injection of sodium nitrite. Upper curve, apex sounds; lower curve, pulmonary sounds (Experiment C 208, X).

ous analysis, the intensity of the heart sounds is fundamentally due to changes in the arterial pressures, and the consequent changes in the height to which intraventricular pressure is elevated during the isometric period of systole, it should be possible to produce such changes without alteration in the heart rate by varying the total resistance against which blood must be pumped. This may be experimentally accomplished in various ways of which the following was utilized in this investigation, viz.: (a) By stimulation of the central vagus which causes a reflex general vasoconstriction. This increases the arterial pressure and, consequently, the height of the left ventricular pressure during the isometric period; (b) by compression of the aorta, which acts similarly, and (c) by the injection of nitrites, which causes a

reduction in arterial resistance, a consequent fall of arterial pressures and a lowering of left ventricular pressure during the isometric interval.

Such systemic changes are not without a secondary effect on the pulmonary and right ventricular pressures. When the total arterial resistance is raised within the arterial system, the left ventricle acts less efficiently as a pumping mechanism and a slight damming back of blood into the pulmonary system occurs. This acts to increase the total resistance in the pulmonary circuit, causes the pulmonary arterial pressure to rise somewhat and increase the pressure in the right ventricle at the end of the isometric period.

(a) *The influence of increasing arteriole resistance by stimulating the central end of the vagus nerve.*—In Figure 4 are shown records before and during the elevation of arterial pressure in this manner. During the elevation of arterial pressure (B) the number and amplitude of the vibrations comprising the first sound increase definitely in all the auscultation areas, indicating an accentuation. In the great

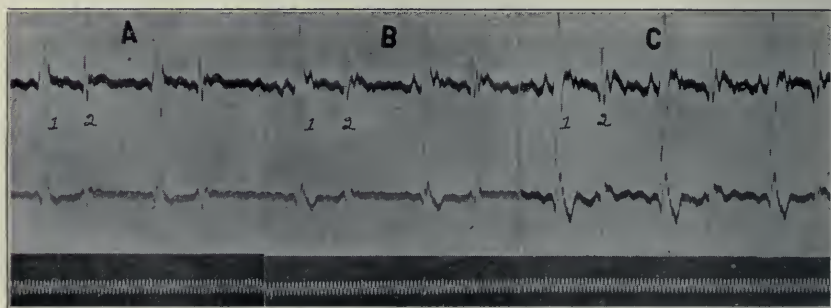


Fig. 7.—(Two-fifths actual size.) Three records of heart sounds showing amplitude of vibrations. A, before; B, during, and C, immediately following rapid saline infusion. The effect started in B continues in C. Upper curve, apex sounds; middle curve, pulmonic sounds; lower curve, tuning fork 0.02 sec. (Experiment C 207, X).

majority of cases, the second sound is also accentuated over the aortic and apex regions, as is well shown in Figure 4. The second pulmonic, though definitely accentuated, increases to a lesser degree.

The relative extent to which the two sounds are accentuated varies greatly in different regions. Over the pulmonary area the first sound is, as a rule, affected most, while over the aortic area, the second sound is predominantly affected. Five minutes after cessation of stimulation (C), the sounds return to normal although the second pulmonic often remains somewhat accentuated.

(b) *The effect of aortic compression on the intensity of heart sounds.*—From a priori considerations we would expect precisely the

same changes in the amplitude of the two sounds as follows central vagus stimulation. As shown in the typical records of Figure 5, this is precisely the case and contrary to the findings of Lewis.<sup>1</sup> The increase in the amplitude of the first as well as the second apical sound is very evident on comparing the second segment (B) with A and C, which are the normal controls before and after compression. While an accentuation of both sounds accompanies a mechanical elevation of arterial pressure, it is quite obvious that the second sound at the apex is accentuated relatively more than the first. In the pulmonic area, the changes in the sounds are not as marked. This is especially true of the first sound, the pulmonary second being somewhat intensified.

(c) *The influence of peripheral dilatation produced by sodium nitrite.*—When sodium nitrite is administered intravenously to an

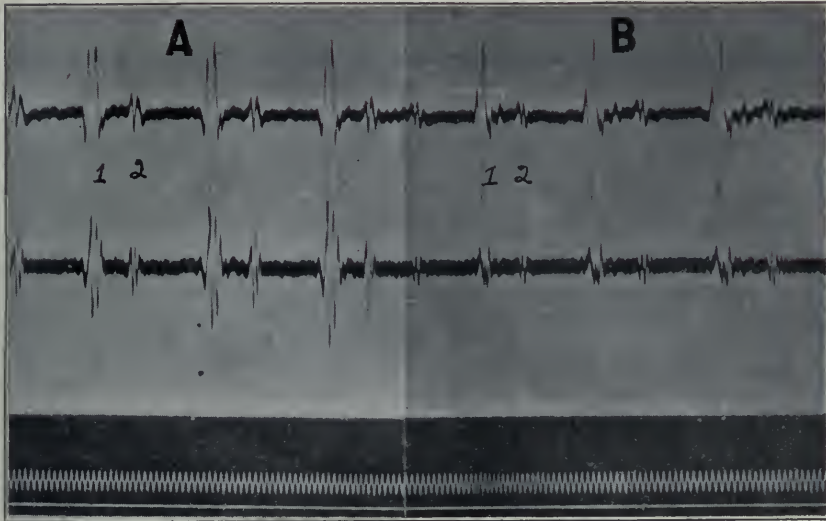


Fig. 8.—(Two-thirds actual size.) Two records of sounds. A, before; B, during compression of the inferior vena cava. Upper record, apex sounds; middle record, pulmonic sounds; lower record, tuning fork vibrations, 0.02 sec. (Experiment C 210, IX).

animal whose vagi nerves have been previously divided, the amplitude of the first and second apex sounds decreases, indicating a reduction in their intensity. A slight, but by no means marked, decrease is also observed in the pulmonary sounds. These changes are well shown in the three segments of Figure 6. Comparison of the relative changes in intensity of the two sounds shows that the enfeeblement of the first sound is greater than that of the second sound.

(d) *Discussion of results.*—These observations confirm the previous conclusion that the intensity of the first sound is related definitely

to the height of the arterial pressure within the pulmonary or systemic circuit and is determined by the height to which the pressure is elevated during the isometric period.

Owing to the fact that the systemic pressure variations are much more extensive in these experiments, they demonstrate much more clearly the relation between the intensity of the second sounds and the height of the arterial pressure. Whenever arterial pressure is raised the second sound augments, and whenever this produces a back effect on the pulmonary circuit, the pulmonary second sound also increases.

It is quite obvious on careful analysis, that the first and second sounds do not always intensify to an equal degree when arterial pressure is raised or lowered through peripheral causes. In the systemic circuit, at least, the rule seems to be that the second sound is predominantly accentuated when the pressure is elevated, while the first is predominantly enfeebled when the pressure is lowered. No explanation entirely satisfactory suggests itself. It is well to bear in mind in this connection that the tension developed during the isometric period, and, consequently, the intensity of the first sound, is determined by the pressure existing at the time that the semilunar valves open (at a, Figure 3). On the other hand, the closure of the semilunar valves is determined by the pressure existing at the very beginning of diastole, e. g., at c, Figure 3. It is quite apparent on reflection that the relative changes of pressure at these two periods may vary independently and to an unequal degree, depending on the particular set of dynamic conditions which operate. Additional work of a very fundamental nature must first be done, however, before a final and satisfactory answer may be given to the question as to why at times the first sound and at times the second sound seems to be affected predominantly.

3. *Influences affecting the systolic discharge of the ventricle.*—Under normal conditions, when the heart rate remains unaltered, the systolic discharge of each ventricle is determined by the volume of blood returning to it during diastole. This also determines the initial pressure (Figure 3, x) which exists within the ventricle at the time it begins to contract, and upon this, in a measure, depends the systolic tension developed within the ventricle itself. By increasing and decreasing the volume of blood returned to the right auricle, it is possible to at once influence the vigor of the right ventricular contraction, and, after a beat or two, also the vigor of the left ventricular contraction.

Such a modification of the venous return may be experimentally produced by the two opposite procedures of (a) rapidly infusing saline solutions into the jugular vein, and (b) clamping the inferior vena cava.

(a) *The influence of rapid saline infusion on the heart sounds.*—Typical sound records of the apex and pulmonary areas before, during and after a rapid saline infusion into the jugular vein are shown in Figure 7, A, B and C, respectively. A comparison of the first sounds in segments A and B indicates that the first sounds are not increased during the course of the infusion when the right heart becomes extremely distended; in fact, the pulmonic first sound may become decreased in amplitude. This is possibly accounted for by the cardiac slowing which is evident. While the mean arterial pressure elevates during infusion, the arterial pressure at the beginning of ventricular ejection is not changed. The reduction of the pulmonary second sound is further influenced by the predominant dilation of the right heart which occurs at the same time.

After injection had ceased, when the heart had recovered its normal rate and dilation was less marked, segment C was recorded. The first

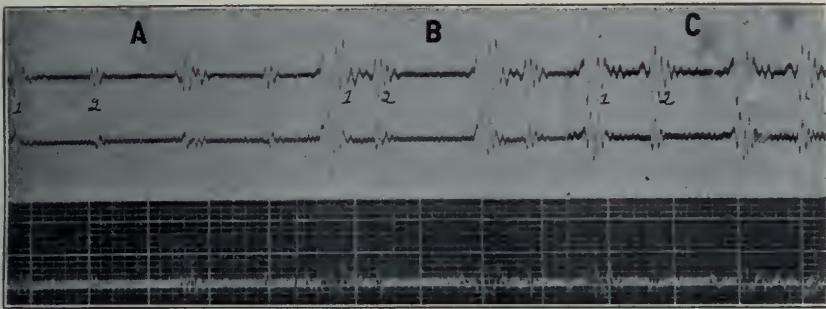


Fig. 9.—(Two-fifths actual size.) Three records showing the relative amplitude of sounds. A, before; B and C, during action of epinephrin. Upper record, apex sounds; middle record, pulmonic sounds, lower record, aortic sounds by Einthoven's phono-cardiograph. Time, abscissae = 0.04 sec. (Experiment C 143, VII).

sound now, true to our anticipation, increases at the apex, and even to a greater extent over the pulmonary area.

The second apical sound, as also the second aortic, increased appreciably in amplitude and number of vibrations as the pressure continued to rise during the infusion. Especially striking, however, is the amplification of the second pulmonic sound. It is noteworthy, also, that during and following such an infusion both pulmonic sounds are affected much more than the aortic or apical sounds.

(b) *The influence on the heart sounds of compressing the inferior vena cava.*—The changes of the heart sounds, before and during compression of the inferior vena cava, are illustrated in Figure 8. While the first and second sounds are both slightly reduced over the apex —

the marked reduction occurs in both pulmonic sounds. These and the preceding experiments where predominant changes in the right ventricle and lesser circulation are evidenced by the greatest variation in the pulmonic sounds are fundamentally important in that they give definite experimental proof (1) that the sounds heard over the left second interspace are really propagated from the pulmonic circuit and right heart, and (2) that valuable information regarding the dynamic conditions of the pulmonary circuits may be gained by comparing from time to time the relative intensities of the heart sounds over different areas.

4. *Influences simultaneously affecting the systolic discharge and total arterial resistance.*—A combination of the cardiac and peripheral factors before studied separately may be induced by intravenous injection of epinephrin into an animal whose vagi nerves have been cut or the terminals of which have been paralyzed by atropin.

(a) *Influence of epinephrin on the heart sounds.*—The changes in the heart following changes in the circulation after injection of epinephrin are very constant. Typical tracings are shown in Figure 9. It is quite evident that the amplitude of the first sound increases to a pronounced degree in all areas. The second sounds are also intensified, but not equally in all areas; the accentuation of the second aortic and of the second apex sound being greater than that of the second pulmonic.

(b) *Discussion.*—Owing to a stimulating effect on the ventricular mechanism, epinephrin causes a greater discharge from each ventricle. This, together with the cardiac acceleration (when the vagi are cut) causes an elevation of the pulmonary arterial pressure and consequently of the right ventricular pressure during the isometric and ejection phases not only, but also produces a higher pressure at the beginning of diastole, i. e., when the semilunar valves close. This accounts for the accentuation of both pulmonic sounds.

In the systemic circuit it causes, in addition, peripheral constriction, which, together with increasing cardiac discharge, causes an enormous elevation of systemic pressure at the end of systole. It may therefore be anticipated that the intensity of the second apex or aortic sound will be very much more augmented than that of the second pulmonic sound. This, as has before been pointed out, proves to be the case.

5. *Influences modifying pulmonary and arterial pressures in opposite directions.*—Finally, it is of great interest to study the relative intensities of sounds from different areas when the pressures in one circuit rise and in the other fall. This may be accomplished by the

use of pituitary extract which has been shown to effect a great rise of systemic pressure and a decline of pulmonary pressure (Wiggers<sup>6</sup>).

In interpreting the changes of the heart sounds during this condition, it is necessary, however, to analyze more precisely the dynamic changes produced in the greater and lesser circulation in more detail.

(a) *The influence of pituitary extract on the greater and lesser circuits.*—Studies of the mean arterial pressures in the pulmonary and systemic circuits,<sup>6</sup> as well as the pressure curves in the right ventricle,<sup>7</sup> have led the writer to insist that the primary effect of pituitary extract on the heart muscle is a depressant one. It causes a decreased systolic discharge which, together with a slower rate, brings about a reduction in pulmonary arterial pressure. The effect on the right ventricular pressure is shown in segments A and B of Figure 10. The pressure

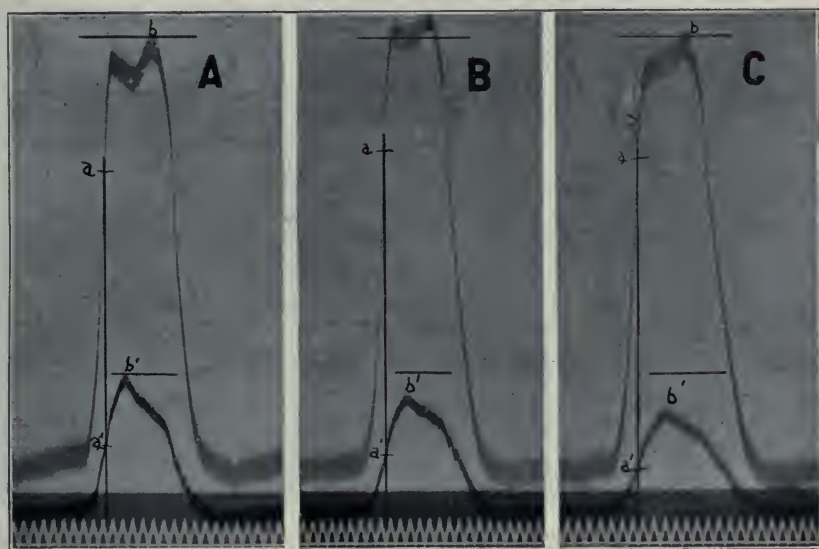


Fig. 10.—(One-half actual size.) Three segments of records showing left (upper curve) and right (middle curve) intraventricular pressure. A, before; B and C, during the stage of pituitrin action. Lower record=tuning fork vibration 0.02 sec. Detailed description in text. (Experiment C 206, XIII.)

during the end of the isometric period, as well as at the height of ejection, is evidently much lower. This is shown in the three segments of Figure 10 a'-b'). The effect on the left ventricle pressure is quite different. Owing to an intensive action on the musculature of the peripheral arterioles, the systemic pressure at once begins to rise. The left ventricle, thereby contracting against a progressively increasing

6. Wiggers, C. J.: Arch. Int. Med. **8**:30 (July) 1911.

7. Wiggers, C. J.: Am. J. Physiol. **33**:394 (Aug.) 1914.

tension, is forced to develop a considerably higher pressure during the isometric phase not only, but during the ejection period as well. This is shown on the three segments of Figure 10, at a and b, respectively.

The total effect of this extract therefore is to reduce the level to which the isometric and ejection pressures are raised in the right ventricle and to increase these levels in the left ventricle.

A study of the relative intensity of the heart sounds over different areas forms almost an experimentum crucis of our former conclusion, for if the intensity of the first sound depends primarily on the height of pressure during the isometric period of systole, and that of the second sound on the height of pressure at the beginning of diastole, then we should find that the intensity of the two pulmonary sounds, on

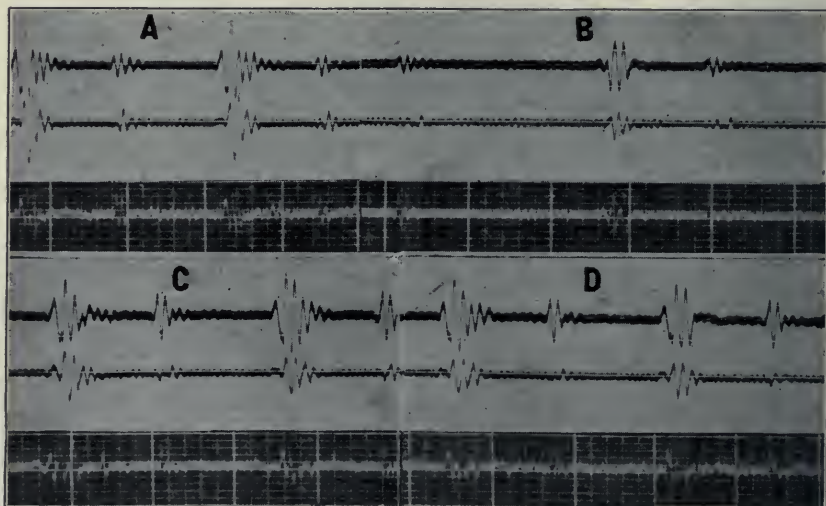


Fig. 11.—(Two-fifths actual size.) Four segments showing the amplitude of sounds. A, before; B, during slowing and first pressure increase following pituitary extract. C and D, subsequently—after marked elevation of pressure and return of cardiac rate to normal. Upper curve, apex sounds; middle curve, pulmonic sounds, lower curve, apex sounds. Time, abscissae, 0.04 sec. Detailed explanation in text. (Experiment C 143, V.)

the one hand, and the apex and aortic sounds on the other, would change in opposite directions during the action of pituitary extract.

(b) *The relative intensities of the heart sounds during the action of pituitary extract.*—Typical effects of pituitary extract on the two heart sounds are shown in Figure 11.

The changes in the first sounds may be considered first. During the rise of pressure (cf. segments A and B) the first sound decreases in all regions. This is, no doubt, due to a lowered isometric pressure

largely occasioned by the great slowing of the heart which complicates the action. The changes are similar to those produced by vagus slowing. As the arterial pressure rises to a maximum 1.2 while the isometric pressure elevates in the left ventricle and falls in the right (curves C and D), the first apical and aortic sounds increase in intensity while the second pulmonic sound decreases in intensity.

Comparison of the normal systemic and pulmonary sounds (segment A) with those occurring during the first cardiac slowing (B) shows that the second pulmonic sound is greatly reduced in intensity, and, in fact, may entirely disappear in some beats, while the second aortic sound is less affected. As the heart accelerates and the maximum pressure is reached within the systemic arteries (segments C and D) the second aortic and second apical sounds are markedly increased in intensity, agreeing with the previous dynamic analysis. The second pulmonic sound, on the other hand, continues to be of smaller amplitude as we should expect from the reduced pulmonary pressure.

#### VI. SUMMARY AND CONCLUSIONS

1. The heart sounds over the apex region, aortic and pulmonary areas were recorded simultaneously or in pairs by the direct sound recording capsules described by Dean and myself. Changes in the intensity of any heart sound over a particular area were determined by comparing the amplitude and number of vibrations entering into that sound complex before and after modified conditions of the circulation were experimentally produced.

2. The intensity of the first sound is not related to the volume of blood discharged by the ventricles, e. g., during slowing of the heart; when the systolic discharge is increased, the first sound is reduced in intensity.

3. The intensity of the first sound over all regions varies directly as the systolic tension developed within the ventricles—and there is good reason to believe, with the tension developed during the isometric period of systole.

4. The intensity of the second sound increases or decreases as the pressure (aortic or pulmonary) at the beginning of diastole.

5. When the pressures at the beginning and end of systole increase, particularly in one circuit and relatively little in the other, an accentuation occurs, predominantly in the sounds referred to the circuit in which the changes predominate.

6. In circulatory conditions where the pressures at the beginning and end of systole vary in opposite directions in the greater and lesser circuits, the intensity of the pulmonary and aortic sounds changes in opposite directions.

7. Direct experimental evidence supplements the anatomical basis for believing that sounds heard over the second left i. c. s. are transmitted from the right heart and lesser circuit, while those heard over the right second i. c. s. and apex have their origin in the left heart and greater circulation.

8. When reserve and caution are exercised, a change in the intensity of the first sound over any area is good evidence of a change in tension developed during systole of the ventricles, while a change in the intensity of the second sound over the aortic and pulmonary areas may safely be used as an index of a change of pressure at the beginning of diastole in the greater and lesser circuits, respectively.

# PROLONGATION OF THE "S-T" INTERVAL OF THE VENTRICULAR COMPLEX AS SHOWN BY THE ELECTROCARDIOGRAPH \*

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The study of electrocardiograms has advanced to a conspicuous degree the recognition of lesions of the heart. At the present time the interpretation of abnormal ventricular complexes is receiving considerable attention, and any observations which may bear on this question give sufficient excuse for their being recorded.

The normal ventricular complex has certain definite characteristics which, on the whole, fall within narrow limits. The main points, in which deviation from the normal may occur, are in the time occupied by the various parts of the ventricular complex and in the form of the deflections constituting this complex. For the sake of convenience the ventricular complex may be divided into two main segments, namely, the Q-R-S period and the S-T period. The Q-R-S period includes the primary deflections starting at the beginning of Q and finishing at the end of S. The S-T period commences at the end of S and terminates at the end of T. The sharp spike-like deflections of the Q-R-S period in the normal electrocardiogram are too well known to necessitate repeated description. The normal T deflection is less constant in its form, and as yet little is definitely known concerning deviations of this spike. The time relations of these two periods are definitely known. In the normal electrocardiogram the Q-R-S period never exceeds 0.1 second, while the S-T period should not exceed 0.28 second. Thus the total Q-T interval in the normal electrocardiogram does not exceed 0.38 second. Although as yet the exact meaning of the T deflection is not definitely decided, it has been demonstrated that the termination of this wave coincides with the beginning of the second heart sound. Therefore it may be presumed that it represents the termination of the ventricular systole.

Animal experiments<sup>1</sup> have demonstrated that lesions of either the right or left branches of the bundle of His produce definite changes both in the form of the ventricular complex and in the duration of its

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\* Read before the Thirty-Fourth Annual Meeting of the Association of American Physicians, June 17, 1919.

1. Eppinger and Rothburger: *Ztschr. f. klin. med.* **70**:1, 1910. Lewis and Rothschild: *Phil. Trans. Roy. Soc., Series B.* **206**:181.

various parts. Carter<sup>2</sup> has reported a series of cases showing changes in the ventricular complex analogous to those obtained by animal experiments and concludes that these are the result of lesions of one or other branches of the bundle of His. He lays down the principles that lesions of this character give the following changes in the ventricular complex.

(a) Q-R-S interval exceeds 0.1 second and, as a rule, constitutes more than one third of the entire complex.

(b) Relative increased amplitude of initial deflections.

(c) Final deflection T usually is in a direction opposite to that of the prominent initial deflection. May be upright or inverted.

(d) Initial deflections almost always show notching in one lead at least. Many bizarre forms are seen.

(e) Final deflection T frequently is much exaggerated.

These points form the basis for determining the gross lesions of the branches of the bundle of His. In a more recent communication the same writer<sup>3</sup> deals extensively with the pathological findings in such cases, not only in regard to the main branches of the bundle of His, but also in regard to the terminal arborizations. Oppenheimer and Rothschild<sup>4</sup> report a series of similar cases with fourteen necropsies, in thirteen of which there was present disseminated patchy sclerosis which was more marked in the left ventricle than in the right. Another important point brought out in their communication was the frequency of closure of the anterior descending branch of the coronary artery. This occurred in eight of the fourteen cases, and in four others there was pronounced diffuse coronary sclerosis.

Robinson<sup>5</sup> has reported a series of cases demonstrating various degrees of abnormal ventricular complexes under diverse conditions. Some of these cases show ventricular complexes which are practically identical with those of lesions of the branches of the bundle of His, while others are not so conspicuously aberrant. The same author has also drawn attention to the frequent temporary character of this condition, indicating that there is not necessarily a definite structural change present. That minor changes in the ventricular complex may indicate abnormal conditions in the ventricle has been demonstrated by Neuhoof<sup>6</sup> in regard to the increased width of the R deflections, which sign he concludes is the result of myocardial degeneration.

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2. Carter, E. P.: *Arch. Int. Med.* **13**:803 (May) 1914.

3. Carter, E. P.: *Arch. Int. Med.* **22**:331 (Sept.) 1918.

4. Oppenheimer, B. S., and Rothschild: *J. A. M. A.* **69**:429 (Aug. 11) 1917.

5. Robinson, G. C.: *Arch. Int. Med.* **18**:830 (Dec.) 1916.

6. Neuhoof, S.: *Arch. Int. Med.* **22**:45 (July) 1918.

Up to the present attention has been chiefly directed to the prolongation of the Q-R-S period. But there is another abnormality of the ventricular complex which has received as yet little or no attention, namely, the prolongation of the S-T interval, and it is with this condition that the present communication is concerned chiefly.

TABLE 1.—CASES MANIFESTING PROLONGATION OF S-T INTERVAL WITHOUT PROLONGATION OF Q-R-S DEFLECTIONS

Case No.	Elect. No.	Age	Cardiac Diagnosis	Transverse Dulness, Cm.	Pulse Rate	Systolic Blood Pressure	P.-R., Seconds	Q-R-S, Seconds	S-T, Seconds	Direction of T to Initial Wave	Preponderance Cornea
1	570	49	Hypertension	15	88	230	0.22	0.09	0.35	Same	Left
2	46	66	Myocarditis	13	95	190	0.16	0.10	0.32	Same	Left
3	112	58	Cardiorenal disease, anginal symptoms	20	100	180	0.20	0.10	0.32	Same	Left
4	307	15	Multiple endocarditis	16	86	120	0.20	0.08	0.34	Same	Left
5	288	58	Myocarditis, anginal symptoms	15	60	180	0.20	0.10	0.37	Same	Left
6*	316	69	Arteriosclerosis	18	58	140	0.19	0.09	0.33	Same	Left
7	317	69	Arteriosclerosis	18	68	140	0.19	0.08	0.31	Same	Left
8	156	40	Cardiorenal disease, anginal symptoms	16	67	210	0.21	0.09	0.32	Same	Left
9	332	67	Myocarditis, anginal symptoms	20	60	170	0.18	0.08	0.34	Same	Left
10	350	35	Mitral endocarditis, anginal symptoms	21	67	195	0.18	0.10	0.31	Same	Left
11	231	55	Myocarditis anginal symptoms	15	75	200	0.16	0.09	0.31	Same	Left
12	151	70	Myocarditis, anginal symptoms	12	54	160	0.20	0.09	0.35	Same	Left
13	110	63	Myocarditis, anginal symptoms	18	60	180	0.18	0.08	0.34	Same	Left
14	42	70	Myocarditis, anginal symptoms	19	75	210	0.18	0.08	0.38	Same	Left
15	328	50	Aortic disease, anginal symptoms	19	75	180	0.17	0.09	0.32	Same	Left
16	41	67	Aneurysm, anginal symptoms	13	65	140	0.20	0.08	0.32	Same	Left
17	312	60	Heart block	18	40	198	—	0.09	0.40	Same	Left
18	312a	60	Myocarditis	43	195	0.2	0.09	0.40	0.40	Same	Left
19	4	70	Arteriosclerosis	43	180	0.4	0.16	0.54	0.54	Same	—
20	19	70	Myocarditis	16	75	190	0.21	0.13	0.36	Same	—
21	23	70	Myocarditis	100	185	0.18	0.10	0.34	0.34	Same	—
22	550	77	Cardiorenal disease, anginal symptoms	20	75	185	0.12	0.09	0.35	Opposite	Left
23	506	38	Aortic valvular dis- ease, anginal symptoms	21	70	140	0.18	0.09	0.32	Opposite	Left
24	409	54	Aortic valvular dis- ease, anginal symptoms	23	86	154	0.16	0.09	0.32	Opposite	Left
25	477	47	Cardiorenal disease, anginal symptoms	24	70	230	0.20	0.10	0.32	Opposite	Left
26	395	58	Aneurysm	16	100	230	0.18	0.10	0.34	Opposite	—
27	561	71	Auricular fibrillation	21	75	200?	—	0.10	0.32	Opposite	Left
28	114	63	Auricular fibrillation, anginal symptoms	21	64	185?	—	0.09	0.32	Opposite	Left
29	394	45	Auricular fibrillation and heart block	17	31	120?	—	0.08	0.46	Opposite	Left
30	429	13	Multiple endocarditis	14	67	85	0.19	0.09	0.35	Same	Left

\* Died of empyema.

#### PROLONGATION OF THE S-T INTERVAL

In Table 1 a number of cases are outlined which exhibit prolongation of the S-T interval without prolongation of the Q-R-S deflections. On analyzing these cases certain points of importance are evident.

1. *Transverse Cardiac Dulness.*—Although percussion is considered by some very competent observers to be a notoriously unreliable method of obtaining accurate data as to the size of the heart, it may be taken at least as a rough guide. In these cases the almost uniform enlargement of the cardiac dulness is most conspicuous. In only four cases is this measurement less than 15 cm. In one of these a child of 13 years of age (Case 26), a transverse cardiac dulness of 14 cm. is most abnormal, and it may be presumed in this case that there is distinct evidence that the heart was enlarged. In the other three cases percussion does not give conclusive proof of this condition. With these exceptions the physical examinations of all these patients would afford reason to believe that cardiac enlargement was the rule.

2. *Left-Sided Preponderance.*—The exhaustive work by Lewis and Cotton on cardiac hypertrophy and the electrocardiographic evidence of the relative preponderance of one side of the heart over the other, affords data for determining this condition. In these cases there was evidence of preponderance of the left side of the heart in all but two of the cases. In both of these the R spike was the principal initial deflection. Although the electrocardiographic evidence was wanting other considerations would lead one to suppose that cardiac hypertrophy did exist and to a conspicuous degree. The cases which do not show typical ventricular complex of left preponderance revealed, however, distinct enlargement of the cardiac dulness. On the other hand, the three instances in whom the cardiac dulness was not conspicuously increased there were typical ventricular complexes indicative of left preponderance. The almost uniform occurrence of electrographic signs of left preponderance coupled with the evidence of increase of the cardiac dulness affords strong presumptive evidence that cardiac hypertrophy existed in all these cases.

3. *Blood Pressure.*—Assuming that cardiac hypertrophy existed in these cases, it becomes necessary to account for such hypertrophy if possible. On investigating the systolic blood pressure<sup>7</sup> it is found that there is a pronounced elevation in eighteen of the twenty-six cases. In all of these cases there was evidence to indicate that this condition had existed for a considerable period. Furthermore, the cardiac diagnoses lend support to this view. All of these cases gave abundant evidence of chronic cardiovascular disease, although in many cases the signs were much greater than the symptoms would lead one to suppose.

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7. The diastolic blood pressure was not always recorded, it has therefore been omitted; although it was uniformly increased in proportion to the systolic pressure.

In the majority of those cases with a normal or low systolic blood pressure other and sufficient reasons were usually present to account for the cardiac hypertrophy. Cases 14 and 26 were children with pronounced evidence of chronic rheumatic endocarditis. Case 6 was a patient suffering from a severe septic condition from which he eventually died. The history in this case was very suggestive of previous hypertension. In Cases 15, 19 and 20 there was evidence of extensive lesions of the aortic valves or the aorta, while in Cases 12 and 25 it was quite apparent that extensive myocardial changes had been occurring for many years. The evidence in favor of pronounced cardiac hypertrophy is almost uniformly present in these cases.

4. *Cardiac Rate.*—Slow cardiac rate is common in these cases. But the length of the S-T period is not constantly in proportion to the rate of the cardiac rhythm. There may be a progressive increase in the pulse rate with an associated diminution in the S-T interval until this reaches a more or less constant duration, and there may be a slight increase of the prolongation with slowing of the cardiac rate. But a variation in the length of the S-T interval without a proportionately conspicuous change in the rate of the cardiac rhythm occurs with fair frequency. Certain cases also show a parallel decrease in the P-R and Q-R-S intervals along with the decrease in the S-T intervals. This would lead one to suppose that this decrease was dependent upon an improvement in the function of the cardiac conduction system, which is comparable to the findings of Robinson in reference to the temporary character on occasion of Bundle Branch lesions.

Cases 5 and 17 (Table 1) also conform to this general improvement in conduction, which is also co-incident with an increase of the cardiac rate. On the other hand, in spite of an increase in the rate to normal, the S-T interval, and to a less extent the P-R and the Q-R-S intervals, do not completely return to the normal time limits.

Many of the cases recorded in Table 1 show a normal cardiac rate, but still there is a pronounced increase in the S-T interval as shown particularly in Cases 1, 8, 11, 12, 13, 18, 22 and 26. If the prolongation of the S-T interval were altogether due to slow cardiac rhythm it would be expected that after long diastolic periods the S-T interval would be greater than after short diastolic periods. This is found not to be so. In a case where there were diastolic periods of great length amounting to 20 seconds, the S-T interval of the ventricular complexes following such long diastolic periods averaged 0.56 second, while the S-T intervals during comparatively rapid periods of the heart's action averaged 0.55 second.

It is reasonable to suppose therefore that prolongation of the S-T interval is not altogether due to slow cardiac rhythm, although this may exert a certain influence.

## CAUSE OF PROLONGATION OF THE S-T INTERVAL

The Q-R-S deflections are now accepted as being representative of the excitation wave passing through the main bundle of His, its main branches and their arborization. The work of Lewis and Rothschild has gone far to prove this theory. They bring forward evidence to prove that the length of time it takes for the excitation wave to appear on the surface of the heart depends upon two factors, namely, the length of the Purkinje tract, and the thickness of the ventricular wall. In the cases here reported it will be noted that the Q-R-S interval is either grossly prolonged, or is in the upper limits of normality, but yet the configuration of the ventricular complexes show little or no change from the normal, except in so far as the signs of left-sided preponderance are concerned. This prolongation of the Q-R-S interval in cases of left hypertrophy confirms a similar observation made by Lewis. This he attributed to the increased thickness of the left ventricular muscle. In certain cases this is not an adequate explanation, as the rapid changes in the length of this period could hardly be dependent upon like changes in the thickness of the ventricular.

Lewis makes the statement that "the length of the initial phases of the bigram may be taken to indicate the duration of the process of activation." Delay of this process of activation may be produced either by injury to one or other branches of bundle division, or by a generally lowered power of conductivity on the part of the conducting system as a whole.

The exact interpretation of the T deflection is not at present settled, but Lewis considers that it is indicative of the decline of the excitatory process. If this be the case, it would indicate that this is considerably retarded in the cases cited above. There is not enough evidence to hand at the present time to determine this question positively. However, the fact remains that there is a distinct prolongation of the ventricular systole which mainly occurs after the wave of activation has been completed. It would appear probable that this were due in part to the increased volume of the muscle, particularly as it has been shown that this has a distinct influence on the length of the activation wave as shown by the lengthening of the initial deflection.

It is well known that when a muscle is fatigued, the contraction time becomes distinctly slower. The heart in all these cases was laboring under a greatly increased burden and was performing the work in a comparatively satisfactory manner. It must be considered to what an extent the prolongation of the ventricular systole (S-T interval) is a compensatory phenomena the result of muscle fatigue.

The question of fatigue is associated so intimately with nutrition, that it was considered probable that some clue to the rôle played by muscle fatigue in producing prolongation of the S-T interval might be

found in cases of malnutrition. Such cases were not at hand, but it was observed that in cases of diabetes during periods of prolonged starvation, or during a very low calory diet, the S-T interval was distinctly delayed. It was found further, that when the diet was increased the S-T interval approached the normal, although it did not necessarily completely return within the normal limits (Table 2). Also it was observed repeatedly that on rest the prolongation of the S-T interval tended to diminish, although in other respects there was little or no change in the patients' condition except for a striking relief from the precordial distress.

TABLE 2.—EFFECT OF DIET ON S-T INTERVAL

Case No.	Elect. No.	Age	Diagnosis	Transverse Dulness, Cm.	Pulse Rate	Systolic Blood Pressure	P-R., Seconds	Q-R-S, Seconds	S-T, Seconds	Direction of T to Initial Wave	Preponderance	Diet
1	268	28	Diabetes	11	73	99	0.18	0.06	0.39	Same	None	5 days starva- tion Full diet
	284				75		0.18	0.06	0.32	Same	None	
2	536	36	Diabetes	13	60	110	0.16	0.07	0.35	Same	Left	1 day starva- tion; 3 days 10 gm. H. Full diet
	555				64		0.16	0.07	0.30	Same		
3	559	29	Diabetes	..	83	115	0.16	0.08	0.32	Same	Left slight	Moderate diet, low fat Full diet
	552				88		0.16	0.08	0.28	Same	None	
4	540	26	Diabetes	12	70	118	0.17	0.08	0.32	Same	None	Moderate diet, low fat Full diet
	553				75		0.17	0.08	0.29	Same	None	
5	535	52	Diabetes	13	92	125	0.15	0.08	0.32	Same	Left	1 day starva- tion; 3 days 10 gm. C.H.
6	537	22	Diabetes	10	70	90	0.17	0.08	0.32	Same	None	1 day 64 gm.; 1 day 30 gm. C.H.
7	538	23	Diabetes	11	66	105	0.16	0.07	0.32	Same	None	Full diet; starved 3 days previously
8	575	67	Diabetes	13	83	120	0.16	0.06	0.30	Same	None	Moderate diet
9	576	5	Diabetes	9	75	80	0.16	0.06	0.29	Same	None	Low diet, no fats
10	577	69	Diabetes	13	72	70	0.13	0.09	0.32	Same	Left	Moderate diet

There were recorded in 65 per cent. of the cases, symptoms which for want of a better term have been classified as "anginal." These were usually characterized by precordial oppression or pain, sometimes radiating to the neck or the left arm. The acute paroxysms of "angina pectoris" were not frequent, although a history of such was sometimes obtained. There was described also a sensation of intense exhaustion. The question arises whether there be an association between the prolongation of the ventricular systole and these symptoms. It is an

accepted physiologic fact that the greater the resistance opposed to the contractile phase of muscular activity, the greater the degree of tension in the muscle. These symptoms usually occurred in cases with an increased systolic blood pressure, or in those showing conspicuous damage to the aortic valves or aorta. Under these circumstances the muscular load would be greatly increased, and as a result the muscular tension likewise. Cases which complain of intense paroxysms of precordial pain do not as a rule show lengthening of the S-T interval, which is suggestive that prolongation of the ventricular systole may be a beneficial phenomena in these cases, and that when it does not occur, cardiac spasm may result from increased work.

#### PROGNOSIS

The prognosis in these cases has been remarkably good in spite of a cardiac condition which frequently gave rise to considerable apprehension. As yet it has been impossible to complete statistics comparing the probable morbidity and mortality of these cases with similar ones without prolongation of the S-T intervals. The fact that none of these cases have died from cardiac failure, while many of them have been under observation for some years, leads one tentatively to consider this condition with favor.

#### CONCLUSION

1. Prolongation of the whole ventricular systole may occur without definite evidence of localized injury to the bundle of His or its branches.
2. Prolongation of the Q-R-S interval occurs with left-sided hypertrophy.
3. Prolongation of the S-T interval may occur with or without lengthening of the Q-R-S period, and is intimately associated with left-sided ventricular preponderance and precordial pain.
4. Similar prolongation of the S-T interval may occur in diabetes, particularly when the individual is on a very low calory diet.

PROGRESSIVE LENTICULAR DEGENERATION ASSO-  
CIATED WITH CIRRHOSIS OF THE LIVER  
(WILSON'S DISEASE)\*

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Our excuse for presenting before the association a case report with its postmortem findings is the rarity of the condition both in America and in Europe. Since Wilson first described the disease in 1912, not more than twenty-six cases have been reported, of which thirteen were observed by various American neurologists. The clinical history of our case was as follows:

REPORT OF CASE

H. B., white, male, aged 22 years, farmer by occupation, was referred by Dr. C. M. Wray of Iowa Falls, and admitted to the medical clinic, Dec. 11, 1916.

*Entrance Complaints.*—Painful cramps in the toes of the right foot and edema of both lower extremities.

*Family History.*—Father died at 45 years of age from tuberculosis of the lungs. Mother is alive and well. There are three brothers, two about patient's age and the third 5 years old, all living and well. One brother died in infancy. Two sisters, one 16 years old and the other 3 years of age, are living and well. The mother denies absolutely any similar trouble in her other children or other members of the family either on the maternal or paternal side. One great aunt died insane. There is no history of alcoholism, epilepsy, syphilis or other hereditary disease.

*Personal History.*—The patient was born and bred in Iowa and had all his life lived in that state or in Kansas or Minnesota. He was a farmer by occupation and of good habits. He used one cup of coffee a day, but no alcohol. He admitted chewing some tobacco and denied absolutely venereal disease. In childhood he had measles, mumps and whooping-cough, but denied scarlet fever, typhoid and rheumatic fevers. He was not subject to winter colds, bronchitis, pleurisy or pneumonia. He denied heart pain, palpitation and shortness of breath. Appetite and digestion were always good. For several years prior to his present illness he had been subject to attacks of diarrhea, lasting for two or three weeks, and usually assigned to some error in diet. The stools never contained blood or mucus. He denied absolutely having had jaundice, abdominal pain, nausea or vomiting. The urinary system was negative, except for slight nycturia. The patient denied headache, convulsions, nervousness or paralysis previous to the present illness. His brother stated that he had always been bright, intelligent and good natured, was popular with his friends and of average business ability. He had never appeared emotional and did not worry unnecessarily. The only accident that the patient recalled was an injury to the back of his neck five years previously, as the result of a kick from a horse; except that he was unconscious

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for about fifteen minutes there were no ill effects. For several years before the onset of his present trouble he had been bothered with cramps in the calves of the legs on first going to bed.

*Present Illness.*—Patient moved to northwestern Minnesota in June, 1916, where he worked on a farm for a Swedish family. His diet was of a general nature, except that meat was not often obtainable. About November 11, following several days of riding on a chain plow, he developed painful cramps in both feet, which were severe enough to cause him to give up his work and return home to Iowa, which he did about November 18. He had no difficulty in getting home by himself, but immediately on his arrival his family noted that he was quite emotional and had marked unsteadiness of his gait, as well as tremor of the hands and head, which gradually increased during his three weeks at home. He next noted gradual swelling of the shins, which was at first assigned to a bruise, the result of a kick from a horse while working on the farm in Minnesota. About Dec. 7, 1916, the family first noticed spasms of the hands, particularly when he grasped an object of which it seemed impossible to let go without assistance from some member of the family. On this account he was constantly watched so that he might be relieved of these painful spasms by relaxing the firm grasp of the patient; this procedure always resulted in immediate relief. Shortly after the swelling of the legs appeared there was also noticed some edema of the hands. There had been no fever, no difficulty with the bladder, no dysphagia and no dysarthria. At the onset of the illness the bowels were inclined to be loose, but recently had been quite constipated. The gait had become increasingly difficult and unsteady, so that he had to be accompanied to the hospital by his brother. His brother was certain that apart from his emotionalism his character was unaltered and that his memory and reasoning ability were good.

*Physical Examination.*—This was made December 12 by Dr. C. P. Howard. The patient is a sick-looking white male of stated age, with flushed cheeks, groaning with pain, which he refers to legs. This is at times apparently increased in severity, making him cry out for a few seconds. There is no characteristic tetanic position of the hands, which are held clinched and often holding the bedclothes. His arms are held almost straight. The thighs are semiflexed at the hips and the legs slightly flexed on the thighs, while the feet are extended to the full. There is no flexion of the toes on the feet. He grimaces a great deal and holds his breath for a few seconds during a paroxysm of pain. There is no Chvostek sign and no Trousseau sign. The upper eyelids are decidedly full and suggest edema. The lower lids are also a little puffy; the left hand seems a little puffy but does not pit on pressure. Both legs, but particularly the left, are edematous and pit on pressure. The skin of the lower leg is reddened and rough; over the left shin is an old scab about the size of a bean, which can be removed readily, leaving a granulating surface underneath; there is little or no infiltration. The skin everywhere is harsh and dry, suggesting that of ichthyosis. In addition there is a sudaminal rash over the chest and arms. The hair of the scalp, chest and arms is thin and fine; it is unusually scanty over the arms, trunk and legs; there are only a few axillary hairs and a sparse distribution of pubic hair, feminine in type.

The external genitalia are fairly well developed; the muscles are soft; the subcutaneous fat is about normal. The thyroid gland is palpable. The head is well shaped and rather small. The hands are not particularly large; the fingers are long and broad.

The chest is large and symmetrical. The lungs are clear throughout.

Heart: The apex beat is not seen but is just felt in the fifth interspace, 7 cm. from the midsternal line. The heart is not enlarged to percussion. The sounds are distant but regular and free from murmurs. The pulse rate is 76, regular, of good force and volume; the blood pressure is 110 mm. systolic and 60 mm. diastolic.

The abdomen is rather distended; the walls are held rigidly, but not board-like; when this rigidity is overcome deep pressure is permitted. Neither liver nor spleen can be felt.

There is no trismus nor risus sardonicus; no spasticity between attacks. The neck is freely movable, as are all the muscles at times. The tendon reflexes of both upper and lower extremities are normal. The abdominal reflexes are present. The plantar reflex is of the flexor type on both sides.

*Blood Examination.*—December 11. Hemoglobin, 110 per cent.; red blood cells, 4,410,000; white blood cells, 6,600; polymorphonuclear neutrophils, 62 per cent.; lymphocytes, 28 per cent.; eosinophils, 8 per cent.; transitionals, 2 per cent.

Blood culture taken and reported negative December 13.

The urine contained a slight trace of albumin, but was negative for sugar, acetone, diacetic acid and microscopically.

December 12. Blood: hemoglobin, 105 per cent.; white blood cells, 5,800. Polymorphonuclear neutrophils, 75 per cent.; lymphocytes, 21 per cent.; eosinophils, 3 per cent.; transitionals, 1 per cent.

In view of the possibility of tetanus, 5,000 units of serum were given intraspinously, 28,000 units intravenously and 8,000 subcutaneously at this time.

The coagulation time of blood was eight minutes and ten seconds (Brodie-Russel).

Cerebrospinal fluid: no cells; Noguchi globulin negative; no increased pressure. Wassermann reported negative December 16.

Serum Wassermann reported negative December 16.

Blood sugar, 0.45 per cent.; blood calcium, 13 mg. per 100 c.c. of blood. The carbon dioxid content of the blood was 38 by the Van Slyke method and 27.9 volume per cent. by the Frederici method.

December 13. The boy seems more emotional today and thrashes about like a hysterical person. The mouth is dry. The throat is red, but with no exudate. The tongue is reddened. Edema of upper eyelids persists; that of the left hand has disappeared and that of lower extremities is markedly less, the left leg barely pitting on pressure and the right much less. The skin over the legs is reddened. There is resistance to passive motion of the right arm and leg, but none of the left arm and leg. On placing one's fingers into his right hand he gradually grasps them firmly and develops a tonic spasm of all the muscles of the extremities, which disappears when the grip is relieved. Trousseau's sign is absent after three or four minutes' pressure. Chvostek's sign is absent over the face and nerves of the upper and lower extremities. The tendon reflexes are not increased.

Dr. Beifeld reports that, owing to resistance of the patient, the electric irritability tests cannot be carried out with any degree of accuracy. He states, however, that it is not markedly increased.

December 14. The general condition is much improved. During our visit he was free from cramps. The edema of the extremities seems much less. The skin shows several *linæ atrophicæ* over the leg. The thyroid gland is just palpable and the trachea can be felt with great ease. Trousseau's sign was a little suggestive this morning.

December 15. The stool was brown in color and semisolid. Meyer's test for occult blood was definitely positive. Microscopic examination was negative.

The patient had a better night. He seems brighter. The edema has disappeared almost entirely even from the right leg. The eyelids are less puffy. He has had an occasional nosebleed. There is still some spasm of the lower extremities, with extension of the feet; there is also slight flexion of the fingers and wrists. On testing for the Trousseau sign the left hand assumes a curious position, more of a claw hammer than the obstetric hand and there are clonic movements of the fingers with apparently voluntary clonic movements of the arms. No Trousseau is present on the right side. No Chvostek sign is present on either side.

December 16. Dr. Beifeld reports that the electrical irritability is not increased.

Dr. L. W. Dean noted some exophthalmos, with von Graefe's sign. The fundi were negative.

Blood: white blood cells, 7,960; polymorphonuclear neutrophils, 68 per cent.; lymphocytes, 29 per cent.; eosinophils, 2 per cent.; transitionals, 1 per cent.

Following ingestion of 200 grams glucose no sugar appeared in the urine in four hours. The carbon dioxide of the blood (Frederici) was 30 volume per cent.

December 17. Last night was the best to date except for profuse sweating. The patient cries out every few minutes during the visit on account of painful cramps in legs. He denies pain in the arms. He claims that cramps are due to the grasping of things with the hands, which is an impulse hard to control. He frequently has periods of noisy breathing, but no periods of apnea. He eats fairly well; has no incontinence of urine or feces; continues to hold arms adducted with fingers flexed. The thumb is usually outside of the palm. The head is moderately retracted, usually turned to the right; no exophthalmus or any of the lid phenomena. The lips are slightly cyanotic. The cheeks are flushed. There is neither facial paralysis, spasm, tremor or Chvostek sign. There is more or less constant choreiform movement of the thighs. The legs are fully extended in talipes equinovarus position even in the absence of spasms. During painful spells the calves are distinctly contracted. The grips measured by the dynamometer are: right, 90; left, 40. He has difficulty in releasing the grip; he cannot elevate the arms above the head but keeps them in a constant swaying motion. The gross strength of the limbs appears normal. The tendon reflexes were all present except both Achilles reflexes which could not be elicited. Plantar and abdominal reflexes are normal. Sensation was intact throughout. The gait was interfered with by spasm of the calf muscles, which causes him to walk on his toes.

December 17. Hemoglobin, 88 per cent.; white blood cells, 14,080. Differential count. Polymorphonuclear neutrophils, 73 per cent.; lymphocytes, 23 per cent.; eosinophils, 4 per cent.

The urine showed a few red blood cells microscopically, but was otherwise negative.

The stomach tube was passed but no gastric content could be aspirated. On lavage the water returned without any solid material and was blood-stained, but the patient was bleeding a little from the nose and gums at times.

December 18. A second attempt for an analysis of a test breakfast was a failure, as the stomach was found to be empty at the end of forty minutes.

The patient was found bathed in sweat and presenting all the signs of a general infection, with slight tendency to cough and an occasional nosebleed. If anything the painful cramps have been more frequent recently. Examination reveals a dry, brown tongue. The heart was negative except for a soft, systolic murmur audible at the apex and over the precordia. The spleen could not be felt. There are still tonic spasms of the arms and legs which are now only painful in the hands. On attempting passive motion there is still definite resistance met with in all the muscle groups of the extremities. A second blood culture was taken today and reported negative on December 20.

The roentgenogram of the sella turcica showed no variation in size or contour from the normal.

December 20. The coagulation time of the blood by the Brodie-Russell method was six minutes.

A second lumbar puncture revealed no increase in pressure, six cells per c.c. and a negative Noguchi globulin test.

December 20. The patient developed incontinence of urine and stools and became very restless. He vomited on several occasions, and finally at 4 p. m. became comatose. One hour later, following a profuse dark emesis, he died.

The case was most obscure throughout its course. Tetany seemed excluded, though we thought of pluriglandular insufficiency and kept investigating along these lines. There was nothing to suggest an organic nerve lesion. He always appeared toxic and toward the end showed evidence of some terminal infection, with suggestive signs of a pneumonia. For three days before his death the temperature varied between 100 and 104 F.; the pulse ranged from 90 to 120 per minute and the respirations from 30 to 40 per minute.

The necropsy findings came as a great surprise. The cirrhosis of the liver was never even suspected. The liver itself was never palpable, and though the dulness was diminished this was assigned to the moderate tympanites present.

*Necropsy.*—December 21 (five hours postmortem), by Dr. C. E. Royce.

*ANATOMIC DIAGNOSIS.*—*Cystic degeneration of the basal ganglia; cirrhosis of the liver, colloid cystic degeneration of the parathyroid glands; bacteriemia; uniform congestion of the lungs.*

The body is that of an adult white male, about 5 feet and 11 inches in length, without deformity. The body is well nourished. Rigor mortis is well established. There is no edema present. The posterior surface of the body is livid. The face is also reddish purple in color, and rather blotchy in appearance. The same is true to a lesser degree of the upper part of the thorax. The skin over the elbows, about the umbilicus and over the left shin, is brown and rather scaly. There is a bloody discharge from the nose. On turning the body on the right side a considerable amount of bloody fluid runs from the nostrils. The superficial lymphatics are not enlarged. The pupils are round, regular and equal, measuring  $3\frac{1}{2}$  mm. in diameter.

On opening the body the abdominal cavity is found to contain about 350 c.c. of serous, slightly blood tinged fluid. The liver is seen to be very nodular. The omentum is thick, reddish yellow in color and rather dense. The peritoneal surfaces are nowhere adherent. The intestines are moderately distended with gas. The appendix is embedded posteriorly to the cecum. No fluid is found in the pleural cavities and there are no adhesions. The pericardial cavity contains 50 c.c. of clear yellowish fluid; no adhesions are present.

*Liver.*—The liver is about the usual size and weighs 1,540 gm. and measures 24 by 18 by 8 cm.; its surface is very nodular, the nodules being nearly uniform in size, varying from 5 mm. to  $1\frac{1}{2}$  cm. and appearing evenly distributed on all the surfaces. The color of the nodules is a rather light grayish brown and the intervening tissue is brown. The cut surface shows that these nodules are evenly distributed through the substance of the liver and are of about the same size and number as were seen on the surface. The tissue of the nodules is rather friable; the intervening tissue is firm. There is no appearance of umbilication present.

*Gallbladder.*—The gallbladder is enlarged and distended. Its surface is a grayish white in color, and only by persistent and severe massage is it possible to express bile into the duodenum. The ducts are found to be patent and without deformity.

*Spleen.*—The spleen weighs 320 gm. and measures  $13\frac{1}{2}$  by  $7\frac{1}{2}$  by 4 cm. It is bluish in color and somewhat mottled, and the capsule appears wrinkled. It is bright red on the cut surface and its consistence is moderately firm.

*Pancreas.*—The pancreas weighs 190 gm. and measures 17 by 6 by 2 cm. and presents the usual lobulated appearance. It is grayish red in color and its consistence is uniformly firm throughout.

*Esophagus.*—The esophagus is regular in size and shape and has a smooth appearance on the inner surface.

*Stomach.*—The stomach contains about 50 c.c. of dark bluish fluid and the inner surface shows some erosions and areas of hyperemia.

*Small Intestine.*—Scattered through the small intestine may be seen patchy areas of bluish color. They measure about 2 by 2 cm., their general shape being square rather than round.

*Large Intestine.*—The large intestine presents on its proximal portion a general grayish-black discoloration of the mucosa, against which the lymphoid follicles appear as lighter colored substance, giving the appearance of trout skin.

*Kidneys.*—The kidneys are slightly larger than usual; the left kidney weighs 220 gm. and measures 12 by 7 by 4 cm., while the right kidney weighs 220 gm. and measures 11 by 7 by 4 cm. The surface of the kidney is smooth and regular. The capsule strips easily. The ratio of the medulla to cortex is as 1 to 2.5. The consistence is uniformly firm.

*Suprarenals.*—These glands are slightly enlarged. The left on section presents an excess of blood in the medulla; the right presents the usual yellow cortex and reddish-brown medulla.

*Ureters.*—The ureters are without deformities and are patent.

*Bladder.*—The bladder is smooth and without reddening.

*Prostate.*—The prostate seems slightly nodular, but is not enlarged.

*Lungs.*—The lungs are crepitant. They are both dark red throughout and exude a red, frothy fluid on section. Excised pieces float in water. Slightly lighter colored areas may be found scattered through the surface of the lungs, which on section are shown to be superficial. The left lung weighs 480 gm. and measures 22 by 14 by 9 cm.

*Heart.*—The heart weighs 290 gm. and was found filled with vermilion-colored liquid blood. The right border measures 10½ cm.; the left border 11 cm. The thickness of the left ventricle is 2 cm.; the thickness of the right ventricle is ½ cm. The muscle is firm, reddish brown in color and the valves are intact, and without deformity. The intima of the aorta and other blood vessels, as far as they were exposed, was reddish brown in color.

*Thyroid Gland.*—The thyroid gland was rather small, weighed 19 gm., was firm and smooth and in every respect appeared normal.

*Parathyroids.*—The parathyroids were readily found and presented no abnormality.

*Testes.*—The testes were both descended and to the naked eye appeared normal.

*Brain.*—The superficial portion of the brain shows an engorgement of all the blood vessels and a rather marked excess of cerebrospinal fluid. On manipulation of the brain a reddish fluid is seen to pour from the severed infundibulum. About 2 cm. of fluid was expressed in this way. The dura appeared normal except for discrete pea sized areas of opacity on its inner surface.

*Pituitary Body.*—The pituitary body is elongated transversely and weighs 920 mg. It is not especially reddened and its consistence is uniformly firm throughout.

The brain and the upper portion of the cervical cord were placed in formalin for five days and were then examined further.

The cerebrum divided horizontally by the Pierre Marie coupe d'élection shows in its lenticular nuclei a bilaterally symmetrical cavitation. The cavitation, however, is not sharply confined to the lenticular nucleus but involves, although to a lesser extent, the internal capsule and the optic thalamus. A few sharply circumscribed cavities are also seen in the white matter of the frontal lobes.

The cavities are sharply defined with smooth walls. The shape of each cavity is roughly oval or circular and the longest measurement of any one will not exceed 1 cm. There is slight grayish red discoloration of the globus pallidus. The putamen seems not to be discolored.

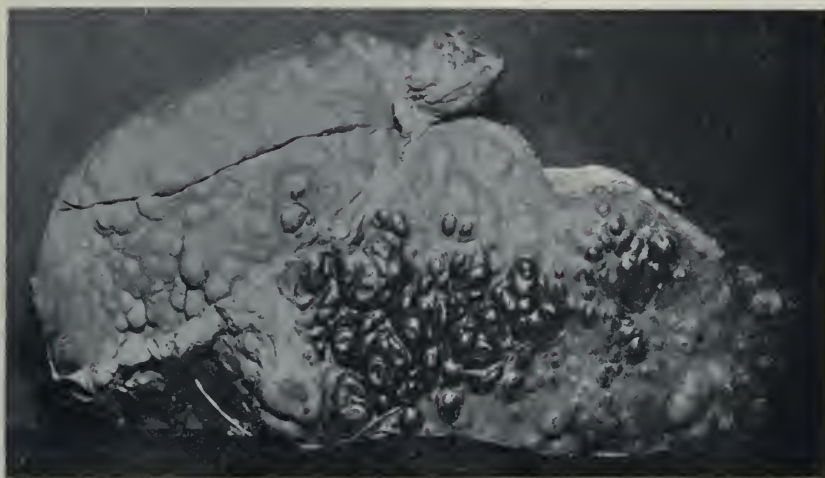


Fig. 1.—The liver.

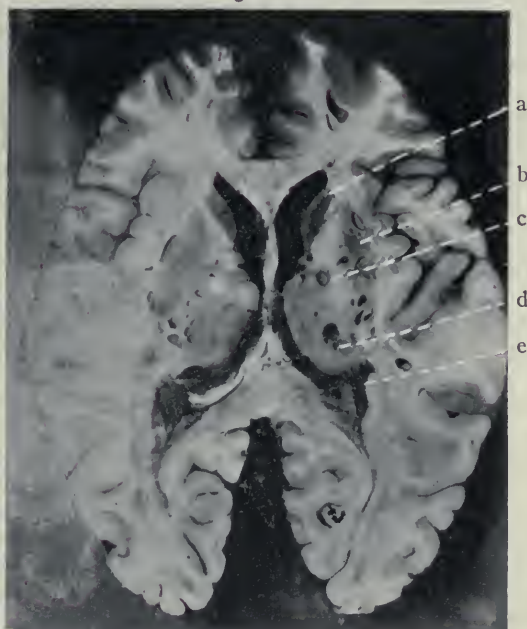


Fig. 2.—Section of cerebrum showing the basal ganglia; a, caudate nucleus; b, putamen globus pallidus of lenticular nucleus; c, internal capsule; d, optic thalamus; e, lateral ventricle.

Otherwise the gross section of the brain presents nothing of comment. Neither in gross nor in microscopic preparations was there any pigmentation that would have suggested bile as its origin.

**HISTOLOGIC DIAGNOSIS.**—*Progressive degeneration of the neuron and glial elements of the basal ganglia, most extensive in the lenticular nucleus but involving the optic thalamus, caudate nucleus, internal capsule and red nucleus and to a slight extent the white matter just beneath the gray matter of the cortex.*

*Chronic interstitial hepatitis; lymphoid hyperplasia manifest in spleen and retroperitoneal lymph nodes. Acute congestion of spleen and kidneys. Colloid cystic degeneration of the parathyroid glands.*

**HISTOLOGY:** *Liver.*—The portions of the liver tissue which appear in the gross specimen as nodules projecting from the surface, on microscopic examination present an approximately normal histologic appearance. The intra-lobular tissue is thickened and infiltrated with leukocytes, many of which are of the polymorphonuclear type. The liver cells of these nodular areas present in some parts large numbers of fat spaces; in others greenish brown pigment granules may be seen. Congestion in these areas is not a marked feature. The tissue outside the nodules above referred to is composed of laminae separated by structures which look like bile ducts, and is everywhere infiltrated with red and white blood cells. Endothelial cells and fibroblasts are also numerous in these portions of the tissue. The leukocytes seen are largely of the small mononuclear variety.

*Spleen.*—The capsule of the spleen is thick and the trabeculae are broad. The finer reticulum of the spleen is increased in density. The pulp contains red blood corpuscles in large numbers. The malpighian corpuscles have their usual appearance and are somewhat overshadowed by large and denser lymphoid areas, in connection with which no blood vessels may be found.

*Pancreas.*—The tissue of the pancreas appears to be more compact than usual. With the higher powers the formation of the acini may be seen, but the cells are so crowded together that in most instances the lumen is not visible. The islands of Langerhans are also dense masses of tissue. In general, the nuclei are small with the cell body large.

A section from one of the large lymph nodes found near the pancreas shows hypertrophy of its constituent parts; the lymph follicles are increased in number. The endothelial linings of the lymph spaces are proliferated and the trabeculae are more dense than usual.

*Kidney.*—The kidney shows congestion and increase of connective tissue. The tubular epithelium is somewhat granular and the tubules are partly filled with granular debris.

*Suprarenals.*—The glands present their usual appearance, except that there is a little less regularity of arrangement among the cords. There is diminution in the size of the cells, so that their number appears greatly increased. The cytoplasm of the cells is dense, staining brightly with eosin.

*Stomach.*—The superficial portion of the mucosa is exfoliated. The epithelium of the tubules is in part missing and the remaining cells appear shrunk. The lymphoid nodules are numerous and dense. The sections from the small intestine show the same loss of epithelium.

*Heart Muscle.*—The cross striation is visible and presents marked irregularities in that the red and dark bands vary remarkably in their width at the thin portions of some fibers. The nuclei are swollen and present at their poles a few yellowish brown granules.

*Lungs.*—Most of the air sacs of the lungs are filled with red blood cells and with serum. There is no infiltration with leukocytes and the walls of the air sacs are not thickened.

*Pituitary Gland.*—The pituitary gland presents its usual glandular structure, without apparent alteration.

*Thyroid Gland.*—The usual histologic appearance of the gland is well preserved. The acini are dotted with desquamated epithelial cells in many instances.

*Parathyroid.*—The blood vessels are distended and engorged with red blood cells. The gland contains many acini, which are filled with colloid and present the same appearance as in the thyroid.

*Testicle.*—Sections from the testicle show the usual histologic structure without alteration.

*Meninges.*—Sections from the meninges at the site of the opacities in the gross preparation show simple fibrous thickening of the membrane.

*Lenticular Nucleus.*—Histologically, the lenticular nucleus differs from the normal in that the glial tissue is greatly rarefied, appearing as a loose meshwork which is varied in its structural size and density. The cells supported by this meshwork are the nerve cells found here in normal brains plus a few leukocytes, some of which are endothelial and some small mononuclear cells. The distribution of these leukocytes is indefinite. The blood vessels are thin walled, but contain large numbers of large rod shaped gram-positive spore bearing bacteria.<sup>1</sup> Weigert-Pal preparations of the lenticular nucleus show almost complete absence of myelinated structure in the affected portions.

*Optic Thalamus.*—A section through the optic thalamus including the border of a cavity shows the cavity to possess no definite lining. The wall, however, is smooth and regular. The tissue adjacent is rarefied by the presence of numerous small cavities which are elongated and tend to a concentric arrangement with the circumference of the large cavity. The nerve cells in this section appear not to be altered. In the walls of some of the blood vessels may be seen numbers of yellowish pigment granules.

*Caudate Nucleus.*—Histologic changes like those of the thalamus are noted, including the yellowish pigment in the walls of some of the vessels.

*Internal Capsule.*—Throughout the entire section imminent disintegration is apparent. Numbers of nerve cells remain intact but numbers are seen which are shadowy. Frequently about these cells the stroma has almost entirely disappeared. No pigmentation is seen in the walls of any of the vessels.

*Red Nucleus.*—Distinct cavities are found here and many more areas where the destruction of tissue has reached a point from which a cavity would have been formed. In these areas of partial destruction the characteristic is numbers of small cavities many of which open one into another and apparently by fusion of these large cavities are formed. Pigmentation is found in the walls of the vessels. As in other portions of the brain tissue where disintegration is in progress nerve cells with shadowy outlines may be seen.

*Crus.*—The sections show an accumulation of leukocytes within the blood vessels, but otherwise no irregularities. There is no loss of myelinated substance.

*Pons.*—The essential nerve structures and the supporting medium appear unaltered. The blood vessels are thin walled, but contain an undue proportion of leukocytes. Some are crowded by endothelial and polymorphonuclear leukocytes. Other vessels are surrounded by a scattering of small mononuclears. There appears to be no loss of myelin sheaths.

*Medulla.*—The medulla presents the same features as the pons.

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1. The presence of the above-mentioned bacilli together with gram-positive diplococci, also clumps and definite chains of cocci is demonstrable in all tissues examined.

*Cord.*—There are no histologic changes in the upper cervical region which was the only portion of the cord removed for examination.

*Cortex Cerebri.*—The cortex is intact in its essential nervous structure. The pia arachnoid is thickened and slightly infiltrated with endothelial leukocytes and small mononuclear cells.

*Cerebellum.*—No changes are apparent in the cerebellum.

#### DISCUSSION OF THE CLINICAL AND POSTMORTEM FINDINGS

Even after leaving the necropsy room we were still completely at a loss for a diagnosis, and it was only after spending some time in looking over the literature that we stumbled across Wilson's<sup>2</sup> paper. It was then perfectly evident that we were dealing with a case similar to that described by Wilson and others. We, therefore, instituted a more careful examination of the brain after it had been hardened in liquor formaldehydi, and were gratified in finding the characteristic changes in the lenticular nuclei, as one can see clearly in Figure 2. The brain has been cut according to the Pierre Marie coupe d'élection method. This reveals a bilateral symmetrical cavitation and atrophy of the lenticular nuclei. As you will see even with the naked eye the cavitation is not sharply confined to the lenticular nucleus itself, but involves, although to a lesser degree, the internal capsule and optic thalamus on both sides. There is a slight grayish discoloration of the globus pallidus.

Anyone conversant with Wilson's paper will immediately recognize the strong similarity to those described as acute cases of lenticular degeneration. So far as can be determined by the history of our case, it ran a shorter course than any heretofore reported. So far as the clinical symptoms are concerned, there is little to note as peculiar from the other cases. Mentally, he was distinctly emotional, but otherwise normal. The peculiar choreiform movement of the extremities, the muscular rigidity and hypertonicity, the painful spasmodic contractions, have all been noted in the cases reported by others. Our case possibly showed more than usual the phenomenon of perseveration, by which we mean a tendency to grasp spasmodically various objects, as the bedclothes, back of a chair and the hands of the examiner, resulting in a painful spasm until disengaged by the nurse or attendant. We were interested in finding this mentioned by Mills,<sup>3</sup> but with this exception, it had not been noted in any other patient but our own. The vasomotor phenomena of redness and edema of the skin were also exceptional, and have only been noted previously by Mills. The examination of the reflexes, both superficial and deep, and of the various forms of sensation, as well as the special senses, was as usual

2. Wilson, S. A. K.: Brain **34**: Part 4, 1912.

3. Mills, C. K.: Neurol. Centralbl. **33**:1266, 1914.

entirely negative. While no special tests were made of the hepatic function, none of the usual signs of hepatic insufficiency were manifest. Wilson and all the other writers constantly confess that even when from their former experience they were on the *qui vive* for signs of cirrhosis of the liver, these were conspicuous by their absence during life. Only in an occasional case has the liver been noted as palpable or decreased on percussion. Very rarely has jaundice been noted.

As regards the postmortem findings, nothing could be more typical than our case, with the exception that the lesion was not absolutely confined to the lenticular nucleus. Wilson, in his original description, is inclined to emphasize the limitation of the process to the putamen and globus pallidus of the lenticular nucleus and to the caudate nucleus, but as one would naturally suppose additional case reports have shown that the process is not always restricted to the lenticular and caudate nuclei. Ours is not the first in which the optic thalamus, and even the internal capsule and motor cortex, have been involved. In others the pyramidal tracts of the spinal cord have shown slight degeneration. Our case, therefore, may be grouped with several others in which, though the brunt of the process has been borne by the basal ganglia, other portions of the nervous system have been affected. As regards the cirrhosis of the liver, there is considerable dispute as to whether it is a true cirrhosis or some other form of degeneration, but most are agreed with Wilson that it must be classified as multilobular or mixed cirrhosis.

Any student of neurology will be struck with the close resemblance between the clinical phenomena of Wilson's disease and that of pseudosclerosis as originally described by Westphal<sup>4</sup> and Strümpell.<sup>5</sup> In fact, many are forced to confess that it is impossible to distinguish between the two diseases until a complete macroscopic and microscopic study of the brain and other portions of the nervous system have been made. In reading over the numerous cases described as pseudosclerosis, one is struck rather by the comparative lack of complete examination of the brain and cord than by the absence of definite pathology in the completely examined cases. In fact, I must agree with various recent writers on this subject, who state that the difference between the two diseases seems to be an anatomical one; that is to say, in pseudosclerosis the process is more widespread; in a pure Wilson case more localized. The involvement of the cortex accounts no doubt for the greater alterations in mentality in pseudosclerosis than in the other condition. But as our case illustrates there appear to be all degrees

4. Westphal, C.: Arch. f. Psychiat. **14**:87, 1883.

5. Struempell, A.: Deutsch. Ztschr. f. Nervenheil. **12**:115, 1898; **14**:398, 1899.

in the extent of the process from that confined entirely to a portion of the lenticular nucleus to a most widespread degeneration of the central nervous system.

We do not wish to be understood to belittle in any way the accuracy and sharpness of the clinical picture drawn by Wilson, being merely anxious to note the self-evident truth that there is no morbid process, however apparently specific and selective, which restricts itself in its production of clinical and pathological phenomena.

As to the pathogenesis, much has been written. Wilson believes that the degeneration of the lenticular nucleus is due to the selective action of some morbid agent on its cells and fibers and found that this morbid agent was in all probability a toxin associated with a hepatic cirrhosis and possibly generated in connection therewith. He drew the important analogy of the occurrence of so-called "Kernikterus" in certain cases of familial icterus gravis neonatorum, "where in spite of the universal bile-staining of the tissues of the body certain collections only of gray matter in the brain show a marked affinity for the circulating poison while others do not." "The parts that are stained deeply are in particular the nucleus lenticularis and the corpus Luysii (among others), while the optic thalamus, for instance, is scarcely stained at all."

What interested me especially in the literature of pseudosclerosis was a small series of cases<sup>6</sup> which presented among other phenomena an annular yellow pigmentation of the cornea in addition to the cirrhosis of the liver and changes in the nervous system. Further, in three cases either diabetes mellitus or glycosuria or a lowered carbohydrate tolerance was noted. The pigment was thought by some to be silver, by others manganese, while one or two have suggested its close resemblance to that pigment seen in hemochromatosis. We would suggest, therefore, that in the future study of all cases of cirrhosis, and particularly of those associated with marked pigmentation as is true in hemochromatosis, a more careful examination should be made of the basal ganglia in particular and of the nervous system in general.

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6. Kayser, B.: *Klin. Monatsbl. f. Augenheilk.* **40**:22, 1902. Anton, G., and Meyer, O.: *Virchows Arch. f. path. anat.* **201**:349, 1910. Salus, R., and Westphal, A.: *Arch. f. Psychiat.* **41**:1, 1913. Fleischer, B.: *Klin. Monatsbl. f. Augenheilk.* **41**:489, 1903. Kubitz, A., and Staemmler, M.: *Beitr. z. path. Anat. u. z. allg. Path.* **60**:76, 1915.

# THE ENERGY INDEX (S. D. R. INDEX) OF THE CIRCULATORY SYSTEM

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Of all that has been said pertaining to the measurable functions of the circulatory system, there are three well-established facts: they are the systolic pressure, the diastolic pressure and the pulse rate. Very much more than this has been proposed by various investigators, but the fact remains that none have met with universal approval.

In this communication I propose the S. D. R.<sup>1</sup> index which is based on these three known factors. The point of systolic pressure represents the culmination of force inaugurated by the systole of the heart. The point of diastolic pressure represents the highest level of sustained pressure during the diastole of the heart. Each pulse beat consists of a systole and diastole. Irrespective of the length of time occupied by the systole and diastole, together they represent the total effort of a single pulse beat. Figure 1 is a graphic representation of six pulse beats.

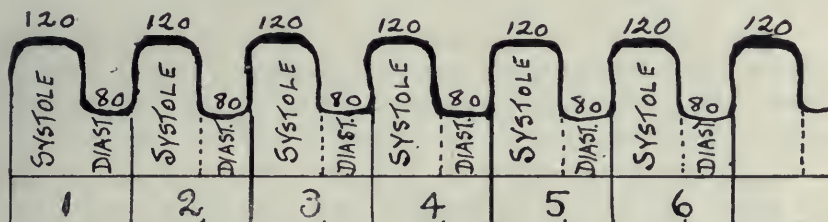


Fig. 1.—Graphic representation of six pulse beats, each beat consisting of a force of 200 mm. Hg.

For example, if in a given case the lifting force of the systole is 120 mm. Hg and the diastolic force is equal to 80 mm. Hg, then the force of the pulse beat which comprises both phases is 200 mm. Hg. This, multiplied by the number of beats, indicates the total force per minute. It should be noted that I use the term "indicates," and not "measures," which may be applied to absolute values.

Now, why this calculation? Simply because neither the pulse rate nor the systolic pressure nor the diastolic pressure taken alone gives us sufficient information. Each element of the triad is constantly changing and adjusting itself to the others — and it is the concerted action of the three forces which maintains the circulatory equilibrium. As

1. Barach, Joseph H.: The Energy Index, J. A. M. A. **72**:525 (Feb. 14) 1914. The Energy Index of the Circulatory System, Am. J. M. Sc. **152**:84 (July) 1916.

is well known, a high systolic pressure is compensated largely by a slowing of the pulse rate. A low diastolic pressure is compensated by an increased pulse rate, and so on. Like the triangle of limited area, alteration in the length of one leg of the triangle results in a change of the other two.

*Effect of Gravity on the S. D. R. Index.*—To illustrate the point, let us take a simple example. Table 1 is based on observations made on forty-eight normal adults. The subjects were placed on a table with a movable top. The first observations of blood pressure and pulse rate were made with the subject in the erect posture. Then the table top was tilted to the horizontal and the second observation was made. After this the table top was again placed in the perpendicular and the third observation was made. The results were as follows:

TABLE 1.—OBSERVATIONS OF RELATION OF POSTURE TO PULSE AND BLOOD PRESSURES

	Erect	Horizontal	Erect
Pulse .....	×	—	+
Maximum Blood Pressure .....	×	+	—
Minimum Blood Pressure .....	×	—	+
Pulse Pressure .....	×	+	—
Venous Pressure .....	×	—	+

This illustrates the adaptation of the three factors which occurs as a result of a mere change in the body posture, with all voluntary effort eliminated. It is the effect of gravity on the function of the circulatory system.

*Effect of Effort on the S. D. R. Index.*—Table 2 shows the effect of graded effort on the S. P., D. P. and P. R. Eighty-two healthy young men did a complete squat at the rate of from thirty-three to fifty times per minute, with the following results:

TABLE 2.—EFFECT OF SQUATTING ON BLOOD PRESSURE AND PULSE RATE

	S.P.	D.P.	P.R.
20 squats at the rate of 33 per minute resulted in	+	—	+
20 squats at the rate of 36 per minute resulted in	+	—	+
20 squats at the rate of 44 per minute resulted in	+	+	+
20 squats at the rate of 46 per minute resulted in	+	+	+
20 squats at the rate of 50 per minute resulted in	+	—	+

The increase or decrease of each of the values is plainly seen. Needless to say, the S. D. R. index showed the effects of the exertion in proportion to the work done and condition of the individual.

*Reaction to Epinephrin; the Test of Goetsch.*—Here the individual, after resting quietly in the horizontal position for half an hour, is given an injection of 0.5 c.c. epinephrin solution, 1:1,000. Depending on

sensitiveness to epinephrin, we produce a certain effect on the circulation, more marked in some than in others. The following two examples illustrate the point:

TABLE 3.—EFFECT OF EPINEPHRIN ON CIRCULATION

Negative Case			Positive Case		
Before Epinephrin	Height of Reaction	After	Before Epinephrin	Height of Reaction	After
S. .... 125 mm. Hg.	136	117	S. .... 108	140	108
D. .... 80 mm. Hg.	82	70	D. .... 70	70	65
R. .... 94 per minute	90	80	R. .... 84	112	84
Index 19,270	Index 19,620	Index 15,160	Index 19,852	Index 23,520	Index 14,532

To offer many more examples of the application of the S. D. R. index is unnecessary. Whenever a change occurs in the activity of the circulatory system, the S. D. R. index will show the change. The S. D. R. index indicates the degree of activity of the circulatory system. It is not intended to measure the work of the heart, although it indicates that better than some of the formulas proposed for that purpose. It does not help us to distinguish the cardiac load from overload, nor cardiac strength from cardiac weakness, nor velocity. What may be said for the index is, that it indicates the amount of energy expended by the circulatory system in the performance of its function, and that it gives us information which we do not get from any one or two elements in the triad.

*The Normal Index.*—In a previous communication based on observations made on 250 normal young men, I designated the upper limit of a normal index as being 20,000 mm. Hg pressure per minute. This was true of young men from 18 to 30 years of age in civil life. If, as we did in the Army, we take large numbers of older men, and include men who, although not perfectly normal according to medical standards, yet were acceptable for military service, we would find that a considerable number would show an index between 20,000 and 25,000. But this group will be made up largely of cases of tachycardia, moderate hypertension and simple cardiac hypertrophy.

*The Energy Index as Found in the Cardiovascular Examination of the Army.*—The figures to be quoted here were obtained from duplicate records made after the examinations were finished and the men had been accepted or rejected. Of the 26,396 men examined in one period of forty-seven days, 1,171 questionable cases were picked out for special examination by our cardiovascular board. This examination was made according to the form B. 1. This examination included the history of the subject, the accurate measurement of the heart, recording of any arrhythmias, the character of sounds and murmurs, taking of blood pressure and the complete exercise test, i. e., pulse in the erect and in the horizontal position, hopping 100 times, taking pulse

immediately after exercise, and two minutes later while the subject is still in the horizontal position. The 1,171 cases constitute all but the apparently perfectly normal ones of the series, including all cases which showed disturbances of rhythm, any abnormal sounds, prominent apex beats, abnormal pulsations, dyspnea, etc. Of these 1,171 men, 996 were finally accepted and 175 were rejected. Of the 175 rejects, 138, or 78 per cent., had an index of not more than 20,000. In other words, if our entire cardiovascular examination consisted only of determining the S. D. R. index, and this compared to the most complete and thorough examination according to the standard of the U. S. Army, we would have been correct in 78 per cent. and incorrect in 22 per cent. of the questionable cases. When we compare the errors into which the S. D. R. index would have led us in the entire series of 26,396 cases, we find the remarkably small figure of 0.05 per cent. This illustrates the value of the S. D. R. index.

TABLE 4.—CASES REFERRED TO THE CARDIOVASCULAR BOARD

	Per Cent.
Tachycardia, simple .....	30.0
Normals .....	26.0
Murmurs without significance .....	9.0
Combined lesions .....	6.0
Hypertrophy with hypertension .....	5.0
Hypertrophy without hypertension .....	5.0
Mitral insufficiency .....	3.0
N. C. A. ....	3.0
Sinus arrhythmia .....	2.6
Extrasystolic arrhythmia .....	2.4
Myocarditis .....	2.0
Mitral stenosis .....	2.0
Aortic insufficiency .....	2.0
Hyperthyroidism .....	2.0
	100.0

Needless to say, the abnormalities in our men were similar to those reported by other cardiovascular examining boards, as Table 4 shows. Furthermore, in searching for the type of case in which the greatest error occurs when the S. D. R. index is used as a guide, I find that in the 22 per cent. of the cases which were accepted by us, and which would have been rejected on the basis of the S. D. R. index, more than three fourths of them were tachycardias. Now, every one who has had to decide as to whether to accept or reject a case of tachycardia, knows how perplexing a problem it is. Probably we erred more frequently in accepting than in rejecting this type of case, expecting that if the man could not perform the duties of a soldier—he would be reclassified later—rather than reject a man who in a few days after the first rush of duties would perhaps return to normal, we accepted him. Later experience showed us that the men with tachycardia whom we accepted were the very ones that showed cardiac insufficiency when they began to experience the hardships of military training.

## DISCUSSION AND CONCLUSIONS

1. The S. D. R. index based on the three known factors of the circulation indicates the state of activity of the circulatory system.

2. Normally, the index is found to be about 20,000 mm. Hg pressure per minute.

3. The index does not indicate "heart disease" or "decompensation" or physical fitness. It designates the amount of effort which the circulatory system is putting forth at the time.

4. A high index means increased cardiovascular effort, either the action of the heart and blood vessels is accelerated because of inability to accomplish their work at a normal rate of activity, or they are fully capable of doing their work, but the resistance to their functioning is great. Either condition is pathologic, and the variation of the index from the normal calls attention to this.

5. A low index means either that the circulation is accomplished with little effort or an inability to expend the necessary effort.

6. Minor changes in the circulation, such as are produced by the slightest alteration in the bodily functions, the effect of drugs, etc., may be detected by the S. D. R. index.

7. The S. D. R. index as a guide to abnormalities in function of the cardiovascular system in a series of 26,396 was correct in 99.95 per cent. In cases referred for special cardiovascular examination, i. e., in the clinically doubtful case, the S. D. R. index proved a correct guide in 78 per cent.

Of the 22 per cent. in which the index failed us, more than three fourths of the cases were tachycardias, and it cannot be said positively that the index was wrong.

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## MENINGOCOCCUS MENINGITIS AT CAMP LEE

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The epidemics of meningococcus meningitis occurring in a number of the army camps have afforded an unusual opportunity for the study of the disease. There have been numerous reports in the literature for the past year emphasizing various phases of the infection.

The disease had previously been studied so thoroughly and carefully by Flexner and his associates at the Rockefeller Institute that the experiences of most observers during the army epidemics have only confirmed previous findings. It seems that the one outstanding contribution to the study of the disease during the past two years is the conception of the infection as primarily a generalized one with a secondary localization in the meninges. For this view we are indebted largely to the work of Herrick<sup>1</sup> and his associates at Camp Jackson where many cases of meningitis have been studied. Workers at other camps have not been unanimous in accepting this view, but Herrick's work has been confirmed in other base hospitals, notably at Camp Beauregard by Landry and Hamley,<sup>2</sup> who subscribe fully to his views. Of course it had long been known that there was a type of the disease fulminating in character in which the infection was evidently generalized. But it had been held that the majority of cases were primarily a localized infection from the outset.

A necessary corollary of the conception of the disease as a generalized infection has been new ideas in regard to treatment. It has been shown that intravenous therapy influences markedly the course and outcome of the disease. This result is well illustrated in the Camp Jackson series of 265 cases. Of 137 patients receiving intraspinal treatment alone 34.3 per cent. died; in 128 cases with combined intraspinal and intravenous therapy the mortality was 14.8 per cent. The point is emphasized also that it is the severe cases in which the newer methods of treatment are most effectual. Mild cases of the disease respond readily to almost any treatment, even spinal drainage alone. It is for the severe cases that we have most needed improved methods of treatment.

Intravenous therapy also decreases the number of intraspinal treatments needed. It has seemed to us that the harm resulting from con-

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1. Herrick, W. W.: *Arch. Int. Med.* **21**:541 (April) 1918; *J. A. M. A.* **71**:611 (Aug. 24) 1918.

2. Landry and Hamley: *Am. J. Med. Sc.* **157**:216 (Feb.) 1919.

tinued intraspinal treatments has not been emphasized enough. The majority of the bad effects of the disease are due to a myelitis in the caudal region and involvement of the nerve roots. This is the direct result of the local introduction of serum and needle traumatism, and is the explanation of the pain and stiffness of back and legs so often complained of. Rosanoff<sup>3</sup> from the study of twenty-six convalescent cases has described what he considers a uniform postmeningitic syndrome. One can see that the most of the symptoms are directly dependent on changes in the spinal cord and nerve roots at the site of the local treatments.

At Camp Lee we have fortunately not had to deal with any large epidemic of meningitis, but cases have developed from time to time, usually in groups. From June 1, 1918, to June 1, 1919, thirty-one patients have been treated in the base hospital.

We have been interested in the analysis of the cases especially from the standpoint of the evidence they present for or against the disease being primarily a generalized infection, and also the results of treatment.

The cases have been quite generally distributed throughout the year and throughout the camp so the epidemic factor has played only a small part. The distribution by months has been as follows: June, 1918, one; July, 1918, one; September, 1918, four; October, 1918, eight; November, 1918, four; December, 1918, nine; January, 1919, three, and February, 1919, one. Every case came from a different company.

Twenty-one of the thirty-one patients, or 67.7 per cent., showed unmistakable evidence of a generalized infection before there were any signs of a localization in the meninges. Fourteen had petechiae, usually in large numbers; one had a macular rash; in thirteen records there is no mention of a rash, and in two cases it was absent. In six cases in which there was no rash the only symptoms for a period varying from seven to twenty-three days were the signs of a generalized infection, viz.: fever, general malaise, joint pains and enlarged spleen, usually with an upper respiratory tract infection of varying degree. The evidence of meningitis did not develop until late, and when lumbar puncture was done there was usually only a small number of cells in the spinal fluid. The meningitis as evidenced by the cellular reaction in the spinal fluid was only of a minor degree as compared with general infection. This type of case has been emphasized by Herrick in a recent paper.<sup>4</sup> The following case illustrates the type as we have observed it here. The generalized infection overshadows the

3. Rosanoff, A. J.: *J. A. M. A.* **71**:1476 (Nov. 3) 1918.

4. Herrick, W. W.: *Arch. Int. Med.* **23**:409 (April) 1919.

local picture. Unfortunately, this patient was treated during the period in which only intraspinal and subcutaneous therapy was being used. The response to treatment was very slow.

CASE 1.—Patient aged 23 years, white, was admitted to the hospital Oct. 16, 1918. His family history was unimportant, and his personal history was negative, except that he had been treated in the base hospital from September 24 to October 4 for influenza and bronchopneumonia. He stated that he had begun to feel badly the night before admission, but had gone to work the next morning. He complained of headache, fever, chilliness, anorexia, pain in joints and backache. The general examination was negative, except that it was noted that he was nervous and irritable. His temperature was 103.2 F., pulse 120, and respiration 24. His temperature was normal for the next three days followed by an irregular temperature for forty-eight hours. October 26 he had a chill with a sharp rise in temperature, and October 29 there was again an unexplained fever of 103 F. Examination was negative, except for a palpable spleen. After several days of normal temperature he was discharged to quarters without satisfactory explanation for his symptoms. November 6 he had headache, general achiness, chilliness and slight vague abdominal symptoms and he was returned to the hospital with a diagnosis of acute rheumatic fever. His temperature was 100 F. The examination was negative, except for tenderness in the right iliac fossa. The next day he had headache and vomiting and twenty-four hours later there was slight neck rigidity, the white blood cells numbered 24,400 and the temperature was 103 F. The Brudzinski sign was negative and the Kernig was only suggestive on one side. Lumbar puncture showed cloudy fluid. The cell count of the fluid from the first puncture is not recorded, but the fluid on the following day showed only 1,018 cells per c.c. He was given 260 c.c. of antineurococcus serum intraspinally and 475 c.c. subcutaneously. Thirteen lumbar punctures were made. He was sent to the Développement Battalion for further hardening, Dec. 19, 1918.

The analysis of the results of treatment in our series is interesting. The cases are divided almost equally into two groups. In the first group, which covers the period from Sept. 15, 1918, to Dec. 7, 1918, intraspinal and subcutaneous treatments were used in twelve cases. Four patients received intraspinal treatment only. We discount entirely the value of the serum given subcutaneously. The mortality in this group was six deaths, or 37.5 per cent.

The second group comprises fifteen cases treated in June and July, 1918, and during the period from Dec. 7, 1918, to March 1, 1919. Eleven patients in this group received both intraspinal and intravenous therapy. Four cases of the mild type, one of which was transferred late in the course of the disease from another camp, were given only intraspinal treatment and recovered promptly. Only one patient of the fifteen died, a mortality of 6.6 per cent. This patient died within thirty-six hours after admission to the hospital.

I realize that no sweeping deductions can be drawn from such a small series, but one in daily contact with the patients could not but be impressed with the good resulting from the intravenous administration of serum. In the second group of cases the patients were on the

average much sicker than those in the first group, and a study of the clinical records convinces us that some of the patients receiving only intraspinal therapy could have been saved by serum given intravenously. In one case reported elsewhere I believe the intravenous injection of glucose was probably the factor determining the outcome of the infection. The value of glucose in reducing the brain volume has been emphasized elsewhere.<sup>5</sup> We believe it is a valuable adjunct as a routine measure in meningitis.

The view is held by some, notably by Neal,<sup>6</sup> that the only value of serum given intravenously is to destroy bacteria circulating in the blood stream. But there must be a passage of antibodies from the blood stream into the spinal fluid through the choroid plexus, and also into the tissues of the central nervous system. And it is really the tissues that are the seat of infection, and not the spinal fluid.

The following case is cited to show the evident effect of serum given intravenously on the affected tissues of the central nervous system and also presumably on the spinal fluid.

CASE 2.—Patient, white, aged 36 years, was admitted to the hospital May 31, 1918, with an evident cerebrospinal meningitis. There was a profuse crop of petechiae and he was very ill. The second day he had an arthritis affecting the left wrist. He at first improved under intraspinal treatment. June 4 he became worse, the spinal fluid was more cloudy and meningococci reappeared. Intravenous injection was attempted but stopped after only a few c.c. had been given because he did not react well. He again became worse on the ninth but then improved and became afebrile. June 27 he began to have fever, headache and vomiting and lumbar puncture showed turbid fluid. After three intraspinal treatments his temperature returned to normal. July 6 he began to have an irregular rise in temperature. He complained of headache but there was no stiffness of the neck or vomiting. On attempting intraspinal treatment again it was found that the spinal fluid had become so thick that it would not run out. Only a few drops could be obtained at each puncture even by aspiration. The introduction of serum had to be abandoned. Meningococci were present in the fluid obtained July 16. Up to this time 440 c.c. of serum had been given in twenty-eight punctures. At this time intraspinal treatment was given up and 435 c.c. of serum given over a course of six days in seven intravenous injections. After each injection there was a reaction with chill and fever. His temperature remained normal after the last treatment. He had a partial paraplegia evidently from caudal and nerve root involvement subsequent to the many intraspinal treatments and was deaf. He was transferred to a general hospital, Oct. 20, 1918, for further convalescence.

The infection in this case which seemed to be localized in the central nervous system was cured by serum given intravenously. A similar case is reported by Camac.<sup>7</sup>

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5. Haden, R. L.: To be published in J. A. M. A.

6. Neal, Josephine B.: J. A. M. A. **72**:1785 (June 14) 1919.

7. Camac, C. N. B., and Bowman, Karl M.: Arch. Int. Med. **23**:17 (Jan.) 1919.

I believe that there is a tendency to overemphasize the danger of the intravenous administration of serum. This is certainly not to be undertaken inadvisably, but in competent hands should be perfectly safe. We have used routinely 100 c.c. at each injection, giving it at intervals of twelve hours for the first three to five doses. The intraspinal treatments have been given twice daily. One of the most fundamental points in the serum therapy is to give it in large doses, the optimum being 100 c.c.

I have been very much impressed by local ill effects of intraspinal therapy. In every case in this series in which a large number of punctures were employed there has been evidence of a caudal myelitis and nerve root injury leaving what bid fair to be permanent residuals. In no case in which intravenous therapy was instituted early has this occurred because much fewer intraspinal treatments were necessary. It has been common to have develop also in those patients receiving many treatments by spinal puncture delirium, increased rigidity, headache and fever for a period of several days. This usually came on well after the period of serum sickness. Dopter<sup>8</sup> ascribes the condition to the mechanical and toxic effects of the reaction leading to the formation of precipitin in the spinal fluid.

The complications in the recovered cases have been as follows: Panophthalmitis, one case; deafness and partial paraplegia, one case; paralysis of sixth cranial nerve and of musculospiral nerve, one case; arthritis (excluding serum arthritis), three cases, and arthritis and paralysis of sixth cranial nerve, one case.

I cannot emphasize too strongly that each case of meningitis must be studied by itself, and all the factors in the case taken into consideration before the plan of treatment is determined. While I believe that every case of meningitis is primarily a blood stream infection when the case is first seen by the clinician, there may be only the evidence of a meningeal localization. If the infection is a mild one it should respond readily to intraspinal therapy. All cases seen early, all with signs of an existing blood stream infection, and all severe cases should have the benefit of serum given intravenously.

#### SUMMARY

Thirty-one cases of meningococcus meningitis have been studied at Camp Lee during the past year.

Twenty-one, or 67.7 per cent., showed unmistakable evidence of a generalized infection before there was a localization in the meninges.

The mortality of the entire series was 22.6 per cent.

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8. Dopter: Quoted J. A. M. A. 71:35 (July 6) 1918.

During the period of intraspinous treatment alone and combined intraspinous and intrasubcutaneous treatment the mortality was 37.5 per cent.; during the period in which intraspinous and intravenous therapy was employed the mortality was 6.6 per cent.

#### CONCLUSIONS

Meningococcus meningitis, in probably every case, is primarily a generalized infection with subsequent meningeal localization.

The use of immune serum intravenously marks a great advance in the treatment of the disease.

Prolonged intraspinal treatment is very apt to result in permanent ill effects from the involvement of the cauda equina and nerve roots.

Intravenous treatment decreases the number of intraspinal treatments necessary, thus minimizing the harmful effects of local treatment.

One case is reported in which an active localized infection in the meninges recovered under intravenous therapy alone.

I am indebted to Major Tasker Howard, Chief of the Medical Service, for the opportunity of studying these cases and for his advice and criticism in the preparation of this report.

## THE CHOLESTEROL CONTENT OF THE BLOOD IN VARIOUS HEPATIC CONDITIONS \*

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In studying the hypercholesterinemia of cholelithiasis, a group of patients was encountered who had a continuous hypercholesterinemia.<sup>1</sup> Even after operation, at which all causes for an obstructive hypercholesterinemia were removed, these patients again became hypercholesterinemic with no discoverable basis for this condition.

In work previously published<sup>2</sup> we gave the evidence for believing that the liver is the regulator of the cholesterol metabolism of the body, the cholesterol being kept at a more or less constant level by excretion of cholesterol through the bile. It is of interest, therefore, to ascertain the cholesterol content of the blood of patients with various disorders of the liver usually associated with icterus.

In obstructive icterus due to cholelithiasis, we have almost invariably encountered a hypercholesterinemia of a rather severe grade. The amounts in the blood varied from 700 mg. to 250 mg. per 100 c.c. The degree of jaundice bore a definite relation to the amount of cholesterol in the blood, indicating that this cholesterinemia is due to the obstruction of the bile duct. However, we have encountered an occasional exception; a jaundiced patient with high temperature and infection will have a lower cholesterol content of the blood than a patient with the same degree of jaundice, but no active infection.

In other conditions associated with icterus, such as cirrhosis of the liver, acute yellow atrophy, pernicious vomiting of pregnancy, etc., the cholesterinemia bears no relation to the intensity of the icterus. The blood in fifteen cases of cirrhosis was examined and gave a maximum content of 0.24 per cent. and a minimum of 0.065 per cent. Only one patient of the fifteen showed a moderate hypercholesterinemia, the amount being 240 mg. per 100 c.c. The figures are as follows for each one of the fifteen patients:

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\* From the Department of Physiological Chemistry, Pathological Laboratory, Mt. Sinai Hospital.

1. Rothschild, M. A., and Rosenthal, N.: The Dietetic Management of Hypercholesterinemia in Cases of Cholelithiasis, *Am. J. M. Sc.* **152**:394 (Sept.) 1916.

2. Rothschild, M. A.: The Relationship of the Liver to the Cholesterol Metabolism, *Proc. New York Path. Soc.*, n. s. **14**:229 (Dec.) 1914.

Per cent.	Per cent.	Per cent.
0.24	0.15	0.125
0.185	0.147	0.105
0.182	0.137	0.1
0.162	0.134	0.075
0.15	0.129	0.065

All of these patients were jaundiced. The extent of jaundice in the cases showing only 0.105 per cent. was greater than in an obstructive cholelithiasis showing 0.64 per cent. The two cases showing the extremely low amounts, 0.075 and 0.065 per cent., were fatal cases, the patients dying three days after the blood examination.

TABLE 1.—CHOLESTEROL CONTENT OF THE BLOOD IN HEPATIC DISORDERS

Cirrhosis Per Cent.	Acute Atrophy Per Cent.	Pernicious Vomiting of Pregnancy Per Cent.	Carcinoma Per Cent.
0.24		0.177	0.4
0.185	0.116	0.164	0.36
0.182	0.1	0.127	0.25
0.162	0.087		0.185
0.15			0.166
0.15			0.162
0.147			0.146
0.137			0.142
0.134			0.125
0.129			0.124
0.125			0.094
0.105			0.09
0.1			
0.075			
0.065			

TABLE 2.—CHOLESTEROL CONTENT OF THE BLOOD IN OTHER ICTERIC STATES

Banti's Disease Per Cent.	Splenomegaly with Icterus Per Cent.	Pernicious Anemia Per Cent.	Leukemia Per Cent.	Chlorosis Per Cent.
0.108	0.1	0.16	0.125	0.103
	0.095	0.155	0.112	
		0.155		
		0.152		
		0.145		
		0.136		
		0.125		
		0.125		
		0.1		
		0.075		

The explanation of these facts is extremely difficult. However, they suggest that in severe disturbances of hepatic function, there is a selective retention of bile pigments, while the cholesterol is not retained. In one case the bile was obtained at necropsy, and showed a rather high content of cholesterol, 0.12 per cent. against a normal content of 0.08 per cent.

In other conditions associated with icterus, such as primary or secondary carcinoma of the liver, or multiple abscesses, as seen in pylephlebitis, the cholesterol content of the blood is not proportionate

to the intensity of the jaundice. In carcinoma of the liver, we have encountered figures varying from 0.4 per cent., to 0.09 per cent.

We have examined the blood of three cases of acute yellow atrophy, and all showed a low blood cholesterin with extreme grades of icterus, the figures being 0.087, 0.1, and 0.116 per cent., respectively.

In three cases of pernicious vomiting of pregnancy with icterus, the figures were 0.177, 0.164 and 0.127 per cent., respectively. All of these cases gave evidence of hepatic disorder, as shown by urinary examination, and all three patients recovered. The blood was obtained toward the end of the disease. It is interesting that these cases showed no hypercholesterinemia, as one ordinarily finds in pregnancy. In the case showing 0.164 per cent. during the disease, a blood examination made two weeks after the patient was well, gave a figure of 0.248 per cent.

Other jaundiced conditions were investigated, those corresponding to the so-called hemolytic types, as seen in Banti's disease, pernicious anemia, chlorosis, leukemias and family splenomegaly with icterus. In all these conditions a normal or decreased content of the blood in cholesterol was noted. However, here we may be dealing with icterus of nonhepatic origin.

#### CONCLUSIONS.

1. In obstructive icterus due to stones, etc., the cholesterol content of the blood is markedly elevated, and bears a definite relationship to the intensity of icterus.

2. In conditions associated with hepatic disorders, the cholesterol content of the blood is not increased, and is usually reduced. The cholesterinemia is not proportionate to the amount of bile pigments present in the blood.

3. In the so-called hemolytic icterus, there is no increase of blood cholesterol.

## THREE CASES OF "RENAL GLYCOSURIA"\*

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Of forty cases of supposed diabetes received at U. S. Army General Hospital No. 9, the following three proved to belong to the class of so-called "renal glycosuria." It was not possible under the circumstances to carry out a comprehensive research, and the observed facts are merely recorded as an addition to existing descriptions of the condition.

### REPORT OF CASES

CASE 1.<sup>1</sup>—Private, infantry, American, 26 years of age, was admitted Nov. 1, 1918.

*Family History.*—The father died at the age of 78 from arteriosclerosis and apoplexy. The mother was drowned at the age of 65. Five brothers and one sister are alive and well. No inheritable disease is known to exist.

*Personal History.*—Patient had measles in childhood. He denies venereal or other diseases. Occasionally he drinks a glass of beer or wine; uses tobacco moderately. He has a normal figure. He has the average habits in diet. His occupation in civil life was shipping clerk. He enlisted May 8, 1917, and sailed for France August 7. He did full heavy duty without difficulty. He suffered somewhat from mustard gas in June, 1918, but did not report sick. In July he received a slight muscle wound in the left forearm from shrapnel and after a week in the hospital a small fragment was removed surgically. This shell exploded about thirty feet away and the patient received no special shock or fright. Glycosuria was discovered in the routine examination at this time. Symptoms of slight pruritus, polyuria, polyphagia, weakness and loss of weight were mentioned in the hospital, but no diet was prescribed and no such symptoms have been present before or since. October 16, he was sent back to America with a diagnosis of diabetes after complete surgical recovery.

*Physical Examination.*—The patient was a tall, well built, muscular young man, with the appearance and actions of perfect health. He was always cheerful and active; free from nervousness or peculiarities. A brown and tanned appearance of the skin over a large part of the trunk and arms was due to mustard gas. An irregular scar of healed shrapnel wound was evident on the left forearm. His teeth were in poor repair. The tonsils and throat were normal. Some palpable cervical lymph nodes were noted. The heart was normal in outline but irregular in rhythm. A diagnosis of incomplete heart block and auricular fibrillation was made by the cardiac service and was confirmed by electrocardiogram. The examination was otherwise negative.

*Laboratory Examination.*—The urine at admission was clear, amber in color, acid, specific gravity 1.036, containing sugar, but no acetone, albumin or casts, blood or other abnormalities. The Wassermann was negative. The blood

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\*From the diabetic service of U. S. Army General Hospital No. 9, Lakewood, N. J.

1. Lieut. L. G. Foster participated in the study of Case 1.

corpuscles numbered 4,700,000; the white blood corpuscles numbered 10,200; small mononuclears, 22 per cent.; large mononuclears, 10 per cent.; polymorphonuclear neutrophils, 63 per cent.; eosinophils, 5 per cent.

*Treatment and Progress.*—The observations made during most of the patient's stay in the hospital are contained in Tables 1, 2, 3 and 4.

### 1. INFLUENCE OF DIET

The patient was kept partly on weighed diets from the diabetic kitchen and was willing and faithful in all respects. During the periods indicated by "regular diet" he ate at the general hospital mess, and also patronized the canteen freely, like the other enlisted men. With the exception of December 9 and the tolerance tests, no special variations of the blood sugar on different diets were observed. The influence of the different components on glycosuria was observed as follows:

TABLE 1.—RESULTS OF URINE AND BLOOD EXAMINATIONS AFTER VARIOUS DIET MODIFICATIONS

Date	Diet			Urine			Plasma	Remarks
	Carbo- hydrate, Gm.	Pro- tein, Gm.	Calo- ries	Volume, C.c.	Glucose, Gm.	Nitro- prussid Test	Sugar, per Cent.	
Nov. 2	125	125	1,100	960	Heavy	Negative	.....	Diet poor in fat
3	125	75	998	1,000	Heavy	Negative		
4	125	75	898	850	2.4	Negative		
5	125	75	898	1,380	6.76	Negative		
6	125	75	898	856	10.67	Negative		Blood taken 11 a.m. and 3 p.m.
7	Fast day			1,600	6.40	Negative		
8	Fast day			1,250	Negative	Negative	0.088	
9	Regular diet			1,100	13.09	Negative	0.100	
10	Regular diet			1,080	Heavy	Negative		Blood taken during digestion at 2:30 p.m.
11	Regular diet			975	Heavy	Negative		
12	0	150	801	1,350	Heavy	Faint		
13	0	150	801	1,250	4.63	Faint		
14	0	150	801	1,425	Heavy	Faint	0.098	Blood taken during digestion at 2:30 p.m.
15	0	150	801	1,400	Heavy	Faint		
16	0	150	801	650	1.50	Faint	0.089	
17	0	150	801	600	1.90	Faint		
18	0	150	801	400	3.00	Faint		Blood taken after breakfast; blood urea, 31.7 mg. per 100 c.c.
19	Regular diet			450	2.8	Faint	.....	
20	Regular diet			1,350	23.70	Negative		
21	Regular diet			1,400	Heavy	Negative		
22	Regular diet			850	8.1	Negative		Phenolsulphonephthal- ein test, 1st hour 35%; 2d hour 18%
23	Regular diet			625	6.4	Negative	0.080	
24	Regular diet			850	10.1	Negative		
25	Regular diet			700	9.3	Negative		
26	Regular diet			875	Heavy	Negative		Blood taken before breakfast
27	Regular diet			950	12.7	Negative		
28	Regular diet			675	10.5	Negative		
29	Regular diet			750	Heavy	Negative		
30	Regular diet			1,025	9.4	Negative		Urine partly lost
Dec. 1	0	Unlimited		425	Heavy	Negative		
2	0	Unlimited		575	4.5	Negative		
3	0	Unlimited		650	4.92	Negative		
4	0	Unlimited		775	5.65	Negative		.....
5	0	Unlimited		275	1.90	Negative		
6	0	Unlimited		575	6.36	Negative		
7	0	Unlimited		675	8.47	Negative		
8	0	Unlimited		550	5.78	Negative		Blood taken at 3 p.m.
9	0	Unlimited		500	3.70	Negative	0.136	

TABLE 1.—RESULTS OF URINE AND BLOOD EXAMINATIONS AFTER VARIOUS DIET MODIFICATIONS—(Continued)

Date	Diet			Urine			Plasma	Remarks
	Carbo- hy- drate, Gm.	Pro- tein, Gm.	Calo- ries	Volume, C.c.	Glucose, Gm.	Nitro- prussid Test	Sugar, per Cent.	
Dec. 10	Fast day			800	3.05	Negative	0.096	Blood taken at 9 a.m.
11	Fast day			1,675	Negative	Negative		
12	0 Unlimited			3,535	16.46	Negative		
13	0 Unlimited			825	15.02	Faint		
14	Regular diet			850	25.08	Very faint		
15	Regular diet			975	14.93	Very faint		
16	Regular diet			1,425	Heavy	Very faint		
17	Regular diet			—	—	—		
18	Regular diet			550	8.75	Negative		
19	Regular diet			725	12.08	Negative		
20	Regular diet			760	5.00	Negative	.....	From December 21 to January 6 away on leave
Jan. 6	Regular diet			150	Heavy	Negative	.....	Urine partly lost
7	Regular diet			625	7.22	Negative		
8	Regular diet			1,200	16.41	Negative		
9	Regular diet			1,075	23.58	Negative		
10	Fasting after breakfast			645	7.31	Very faint		
11	Fast day			625	2.09	Very faint		
12	Fast day			1,325	2.12	Very faint		
13	Fast day			900	1.80	Moderate		
14	Fast day			825	1.65	Faint		
15	Fast day			1,255	Negative	Slight		
16	0 51.2 357			1,725	Moderate	Slight		
17	0 138.8 913			—	—	—	.....	Steak, 250 gm. diet for day
18	Regular diet after p.m.			750	8.41	Moderate	.....	Meat, 600 gm. diet for day, one meal
19	Regular diet			655	9.42	Negative		
20	Regular diet			800	15.71	Negative		
21	0 78.5 2,888			350	3.85	Negative	.....	Bacon, 100 gm., butter, 50 gm., egg yolk. 500 gm. in one meal (break- fast). Urine volume incomplete
22	Regular supper			475	11.30	Negative		

(a) *Influence of Carbohydrate.*—On low calory diets the glycosuria was apparently higher with carbohydrate included (Table 1, November 3, 4, 5 and 6) than with it excluded (Table 1, November 12 to November 18). With unlimited calories there was less glycosuria on carbohydrate free diet (Table 1, December 1 to December 9) than during the various periods of mixed diet. An exception is seen in the high excretion on carbohydrate free diet (Table 1, December 12 and 13) following fasting. The tolerance tests (Table 2) show the production or increase of glycosuria by glucose feeding.

(b) *Influence of Protein.*—Table 3 shows the production of glycosuria and on January 17 of hyperglycemia by eating beefsteak, but the effect is far less than that of preformed carbohydrate. The after-effect of different diets also seems significant. After a period of restriction to 125 gm. each of carbohydrate and protein, glycosuria ceased with two days of fasting (November 7 and 8). After a carbohydrate free period in which protein was eaten in large quantity, glycosuria also ceased with two fast days (December 10 and 11). After mixed diet with unlimited carbohydrate, five days of fasting was

TABLE 2.—RESULTS OF GLUCOSE TOLERANCE TESTS

Date	Time	Urine		Plasma Sugar, per Cent.	Remarks
		Volume, C.c.	Sugar, Gm.		
Dec. 12	9:30 a.m.	500	Negative	0.09	Taken after fasting 2 days
	10:30 a.m.	205	Negative	.....	Drank 200 c.c. water
	11:30 a.m.	335	Negative	0.10	Drank 200 c.c. water
	12:30 p.m.	300	Negative	0.10	Given 100 gm. glucose in 200 c.c. water
	1:30 p.m.	160	0.88	0.214	Drank 200 c.c. water
	2:30 p.m.	370	6.66	0.320	Drank 200 c.c. water
	3:30 p.m.	535	4.82	0.200	Drank 200 c.c. water
	4:30 p.m.	260	2.34	0.170	Drank 200 c.c. water
	5:30 p.m.	125	0.66	—	—
	6:30 p.m.	170	Faint	0.130	Drank 200 c.c. water
	7:30 p.m.	40	Negative	—	Drank 200 c.c. water
	8:30 p.m.	90	Negative	0.090	—
	9:00 p.m.	...	.....	.....	Ate all the bacon and eggs he could
	10 p.m. to 4 a.m.	400	1.04	—	—
Dec. 17	9:30 a.m.	92	0.89	0.100	Taken after 3 days of regular diet
	10:30 a.m.	74	2.36	0.106	Given 100 gm. glucose in 200 c.c. water
	11:30 a.m.	65	1.76	0.080	Drank 200 c.c. water
	12:30 p.m.	65	0.27	0.070	Drank 200 c.c. water
	2:30 p.m.	150	0	0.079	Drank 200 c.c. water
	5:30 p.m.	...	....	0.090	—
Jan. 18	9:30 a.m.	200	0.90	0.088	Taken 5 days after fasting and 2 days on carbohydrate-free diet
	10:00 a.m.	—	—	0.167	Given 100 gm. glucose in 200 c.c. water
	10:30 a.m.	300	3.00	0.214	Drank 200 c.c. water
	11:30 a.m.	200	9.00	0.185	Drank 200 c.c. water
	12:30 p.m.	300	4.29	0.136	Drank 200 c.c. water
	1:30 p.m.	255	1.15	0.116	Drank 200 c.c. water
	2:30 p.m.	150	0.44	0.088	—
Feb. 3	9:30 a.m.	105	Moderate	0.107	Taken after 2 weeks of regular diet
	10:00 a.m.	150	Moderate	0.133	Given 100 gm. glucose in 200 c.c. water
	10:30 a.m.	25	Heavy	0.142	—
	11:30 a.m.	None	—	0.158	—
	12:30 p.m.	50	Heavy	0.101	—
	1:30 p.m.	35	Heavy	0.086	—
	5:00 p.m.	80	Moderate	0.115	—

TABLE 3.—RESULTS OF PROTEIN TESTS

Date	Time	Urine		Plasma Sugar, per Cent.	Remarks
		Volume, C.c.	Sugar, Qualitative Test		
Jan. 16	9:35 a.m.	200	Faint	0.100	Two bloods fasting and urines for the period. At 12 noon fed protein meal, 250 gm. steak
	10:45 a.m.	106	Negative	0.102	
	12:00 noon	32	Negative	—	
	12:55 p.m.	38	Slight	0.097	
	1:35 p.m.	325	Slight	0.115	
	2:35 p.m.	175	Slight	0.107	
	3:35 p.m.	250	Negative	0.122	
	5:00 p.m.	150	Negative	0.075	
Jan. 17	8:30 a.m.	96	Faint	0.094	Two bloods fasting and urines for the period. At 10:20 a.m. fed protein meal, 600 gm. steak
	9:30 a.m.	40	Faint	0.113	
	10:20 a.m.	40	Faint	0.106	
	11:20 a.m.	40	Faint	0.114	
	12:30 p.m.	90	Slight	—	
	1:30 p.m.	96	Slight	0.140	
	2:30 p.m.	135	Slight	—	
	3:30 p.m.	85	Slight	0.129	
	4:30 p.m.	90	Slight	—	
	5:30 p.m.	100	Slight	0.124	
	7:30 p.m.	95	Slight	—	
	8:30 p.m.	—	—	0.109	

necessary before sugar freedom was attained January 15. Hypothetically, the smaller immediate effect of protein is explainable on the assumption that not all the carbohydrate theoretically derivable from it is necessarily formed from it in metabolism, and the smaller after effect by the well-known fact of the smaller glycogen storage from protein as compared with carbohydrate. The observation is interesting as indicating that stored material affects the glycosuria.

TABLE 4.—RESULTS OF FAT FEEDING EXPERIMENT\*

	January 21			Remarks
	8:45 a.m.	12:30 p.m.	3:30 p.m.	
Plasma sugar, per cent. ....	0.105	0.100	0.100	9 p.m. finished large fat meal consisting of bacon, 100 gm.; butter, 50 gm.; egg yolks, 500 gm. Urine up to 10 p.m.; volume, 350 c.c.; sugar, 3.85 gm.
Corpuscle sugar, per cent. ....	57.8	48.5	46.0	
Qualitative lipemia .....	Negative	Faint	Slight+	
Total fat:				
Whole blood, per cent. ....	0.62	0.78	0.79	
Plasma, per cent. ....	0.84	0.90	0.84	
Corpuscles, per cent. ....	0.68	0.67	0.74	
Total fatty acid:				
Whole blood, per cent. ....	0.51	0.54	0.52	
Plasma, per cent. ....	0.59	0.64	0.60	
Corpuscles, per cent. ....	0.46	0.43	0.44	
Cholesterol:				
Whole blood, per cent. ....	0.24	0.25	0.25	
Plasma, per cent. ....	0.25	0.26	0.24	
Corpuscles, per cent. ....	0.22	0.24	0.26	
Leecithin:				
Whole blood, per cent. ....	0.48	0.45	0.45	
Plasma, per cent. ....	0.45	0.45	0.43	
Corpuscles, per cent. ....	0.50	0.45	0.48	

\* Total fat, cholesterol and leecithin are determined directly. Total fatty acid = fat — cholesterol (Bloor).

(c) *Influence of Fat and Total Calories.*—No experiments with pure fat or alcohol ingestion were performed. The disappearance of glycosuria on fasting is more probably explained by the simple withdrawal of carbohydrate than by a fall in total metabolism. In comparing differing diets it is seen that the glycosuria in the low calory period (Table 1, November 3, 4, 5 and 6) is fully as high as could be expected in comparison with the periods of unrestricted diet, considering the much larger carbohydrate intake in the latter; and on carbohydrate free diets the glycosuria in the low calory period (Table 1, November 12 to November 18) compares well with that in the high calory period (Table 1, December 1 to December 9), considering the larger quantities of protein eaten in the latter. Therefore, as far as the observations permit judgment, there is no indication of an influence of the total caloric ration, aside from the portion represented by the direct carbohydrate forming foods.

## 2. PLASMA SUGAR

This was determined by the Benedict method, and was regularly below or near 0.1 per cent. Fractional urine specimens were taken so often as to leave no doubt that glycosuria actually occurred at this

level. Protein ingestion or carbohydrate free diet seemed to create a tendency to hyperglycemia. The single high blood sugar of Table 1, December 9, occurred on carbohydrate free diet. Other observations are mentioned in the two following paragraphs.

### 3. GLUCOSE TOLERANCE (TABLE 2)

The patient took 100 gm. glucose on an empty stomach on occasions when the diets of the preceding days had been different. December 17, after three days of ordinary mixed diet, there was no rise, but instead a slight fall in the plasma sugar. February 3, after two weeks of mixed diet, the curve rose to about a normal height, but was atypical in that the peak came at the end of two hours. December 12, after fasting, the behavior was radically different and the hyperglycemia reached 0.320 per cent. January 18, after carbohydrate free diet, there was again hyperglycemia, but to a less marked degree. The two curves first mentioned are uncommon, but not peculiar to this condition. They represent some abnormality in the patients who show them, but whether this pertains to absorption or metabolism is not always clear. The hyperglycemia in the two curves last mentioned is nothing extraordinary. The increased tendency to hyperglycemia and glycosuria resulting from fasting is a long familiar fact, and there are a few observations of a similar effect of carbohydrate free diet. No confusion should exist between this and the other fact that fasting and carbohydrate free diet are used to increase the carbohydrate tolerance in diabetes. The carbohydrate sensitiveness of the normal fasting organism is a trivial phenomenon, evidently expressing nothing more than some state of temporary unpreparedness for the carbohydrate flood. The actual assimilation of carbohydrate is limited only by the dose. In diabetes carbohydrate metabolism is fundamentally impaired, and is strengthened through the rest afforded by carbohydrate free diet and still more by fasting.

### 4. PROTEIN INGESTION

On January 16 (Table 3) 250 gm. beefsteak gave rise to slight glycosuria without hyperglycemia. January 17, 600 gm. steak caused a more distinct rise of blood sugar, but the glycosuria was still too slight to warrant titration by ordinary methods. December 12 and 13 (Table 1) there was exceptionally high glycosuria with carbohydrate free diet, presumably because the patient either ate more protein or was sensitized to it by the preceding fast.

## 5. RENAL THRESHOLD

It would have been desirable to make a more detailed study of this point, but the existing observations are opposed to the idea that the blood sugar level was the sole factor determining either the occurrence or the quantity of sugar excretion. In the tolerance tests this was evidently greatest when the blood sugar was high (Table 2), but was higher January 18 than December 12, though the hyperglycemia was higher December 12. In Table 3, it is evident that the qualitative urinary reactions do not correspond accurately to the levels of blood sugar; also the excretion was trivial throughout, though the blood sugars\* after these protein meals were often higher, notably January 17, than during the marked glycosuria of the glucose tests, especially December 17.

## 6. URINE VOLUME

On the whole, there was oliguria, sometimes so marked that the patient was led to inquire about it himself. No indication was found of any cause other than a failure to drink. Whenever more fluid was taken on instructions or accidentally, the twenty-four hour urine increased in proportion, and the body weight never indicated fluid retention.

## 7. GLUCOSE AND WATER DIURESIS

In Table 1 no relation is perceptible between the volume and sugar content of the urine, in the sense either of polyuria or oliguria caused by sugar, or a flushing out of more sugar by increased urinary volume. In the glucose tests (Table 2) the water intake was regulated except February 3. The two tests with hyperglycemia showed the following: December 12 a fall in urine volume accompanying the hyperglycemia and slight glycosuria of the first hour after the glucose dose; in the ensuing hours polyuria, roughly parallel to the hyperglycemia, but not to the urinary sugar; then marked oliguria after hyperglycemia and glycosuria had subsided. January 18, less hyperglycemia and less polyuria, though the urinary sugar was greater than December 12, and a less marked diminution of urine after the blood sugar had fallen. December 17, with no hyperglycemia, but moderate glycosuria (the percentages of urine sugar running higher than December 12) there was striking oliguria, with a moderate increase in volume in the 2:30 p. m. specimen when glycosuria had ceased, the whole experiment being characterized by water retention even exceeding that of normal persons. In general, therefore, the urine volume seemed to be influenced by the blood sugar but to be independent of the urinary sugar.

## 8. RENAL FUNCTION (TABLE 1)

The blood urea of 31.7 mg. per 100 c.c. November 16 is a noticeably high figure, though probably affected somewhat by the carbohydrate free diet. November 19 the phenolsulphonephthalein elimination was 35 per cent. in the first hour and 18 per cent. in the second hour.

## 9. CHARACTER OF SUGAR EXCRETED

Fresh urine samples were taken, along with those from patient No. 2, to Dr. P. A. Levene, who prepared and identified glucosazone, and excluded the presence of disaccharids, levulose, pentoses and glycuronic acid. In this hospital, the routine reduction tests with Benedict's solution were sometimes fairly normal in appearance, sometimes slow and atypical. In titration with Benedict's quantitative reagent the end points were satisfactory. Fermentation with Fleischmann's yeast was prompt and complete in tests made at intervals throughout the stay in hospital, except for one short period when a few negative or incomplete fermentations were obtained. These were not thoroughly controlled, and may therefore represent mistakes of some kind.

## 10. BLOOD LIPOIDS

According to Bloor, normal fasting blood contains, in whole blood, plasma and corpuscles, respectively, as a maximum 0.41, 0.43, 0.45 per cent. fatty acids; 0.25, 0.31, 0.23 per cent. cholesterol, and 0.33, 0.26, 0.44 per cent. lecithin.

Table 4 shows that the cholesterol was normal in this patient, not elevated as in the more severe grades of true diabetes. It did not increase during digestion of a meal rich in cholesterol. The lecithin was elevated to a degree comparable with many diabetic cases, but failed to rise during digestion. The fasting values for total fat and fatty acids are normal, but the absence of a digestive increase is remarkable. A slight turbidity of the plasma developed during digestion, but Bloor and Gray have shown that this is not a reliable index of chemical lipemia.

CASE 2.—Lieutenant, ammunition transport service, American, married, aged 42, was admitted Nov. 1, 1918.

*Family History.*—Father, mother and one brother are well. There was no history of inheritable disease in family.

*Personal History.*—Patient had measles, mumps, chickenpox, scarlet fever and whooping cough in childhood; diphtheria in 1892; no other infections. He had no venereal diseases. He used no alcohol, and tobacco only in moderation. He subsisted on an ordinary diet. He had been an investment banker in civil life and lived under the best hygienic conditions. He had a nervous temperament, but never manifested it to a marked degree. He was a member of the National Guard, and served three years in the Philippines, where

he sustained a Mauser bullet wound of the right leg in 1900. This healed uneventfully. He resumed civil occupation until commissioned a first lieutenant, May 10, 1917, and after doing full duty in this country for a year went overseas in May, 1918.

*Present Ailment.*—July 27, 1918, the patient was bringing up several truck loads of small arms ammunition to the battle line at Chateau Thierry, he himself sitting beside the driver on one of the trucks. They were located by a German aeroplane and the entire convoy was destroyed by a heavy concentration of artillery fire, the patient and two other badly wounded men being the only ones to escape alive. The high explosive shell which wrecked his truck killed the driver and hurled the patient to a considerable distance. While being carried to a French evacuation hospital he was wounded with shrapnel and gassed with phosgene. His surgical injuries included superficial wounds and abrasions of feet, hands and back, and severe concussion, especially of the base of the spine, on which he apparently had landed when blown from the truck. He was unconscious for three days. Thereafter his mind was clear, with no hallucinations or loss of memory, but he was weak, and suffered much pain, especially on attempted movements. He was extremely nervous and apprehensive, and had extreme tremor and incoordination, especially when nervous, the muscles of speech being involved like those of the extremities. This condition continued with little improvement, while the patient was moved from one hospital to another. Finally, he was given careful examination at a base hospital, where glycosuria was found and the diagnosis of traumatic diabetes was made, which was assumed as a factor in his unfavorable progress. After confirmation of the diagnosis by higher staff officers in another hospital, the patient was sent to America, Oct. 9, 1918. Important in connection with the glycosuria is the fact that the urine was found free from sugar when the patient received his commission and again when he was examined for overseas duty. Also, in civil life he had been intimate with a young physician, who for incidental reasons had repeatedly tested the urine and found no sugar or other abnormalities. Also after the injury glycosuria is said to have been absent sometimes, generally slight, and heavy especially when there was nervousness.

*Physical Examination.*—The patient is rather short and stout, 5 feet 6 inches in height, weighing ordinarily 160 pounds (now the same). He has an excellent color and a generally healthy appearance, except for nervous manifestations. The general examination is negative. The pupils are equal and react normally to light and distance. The knee and other reflexes are exaggerated, the response sometimes being in the form of clonus. The patient can barely stand and walk with the aid of an attendant and a cane. The stooped posture, gross tremor of the limbs, and shuffling unsteady gait are much like paralysis agitans. He is emotional and excitable ordinarily, and hesitates somewhat in speech because of difficulty both in finding and in forming words. Any sudden noise, such as a fire gong, an automobile horn, or even the slamming of a door, throws him into a panic of helplessness and tremor, in which he is powerless to control his muscles or utter an intelligible word. Even more than of the incoordination and nervousness, he complains of pain in different parts of the body, particularly along the spine, also of headache and insomnia. Orthopedic examination showed tenderness of both muscles and bones in the affected regions, but no displacements, atrophies or other definite abnormalities.

*Laboratory Examination.*—The urine at admission was of a clear amber color, acid, specific gravity, 1.025; containing a copper reducing substance, but negative for albumin, acetone and indican. The sediment showed microscopically a little epithelium and amorphous material, no casts. Later urine specimens were tested repeatedly in the hospital and were the same in general character. The blood Wasserman was negative.

*Treatment and Progress.*—The patient was admitted late in the afternoon of October 25, after having taken a full mixed diet up to that time. He received only soup, coffee and two bran-agar muffins for supper, and the same for breakfast the next morning. The moderate sugar reaction present at admission diminished to a trace, but the copper reduction was slow and atypical. It being suspected that the case was not a true diabetes, the fasting program was broken off by a test meal at noon, high in carbohydrate (cereal, milk, sugar, egg, potatoes, bread, butter, jam). The quantities were not measured, but the patient, being hungry, ate heartily. The analyses disclosed the following findings:

TABLE 5.—PLASMA AND URINE SUGAR IN RELATION TO EATING

Time	Plasma Sugar, per Cent.	Urine Sugar
Before eating .....	0.125	Trace
One hour after eating.....	0.145	Faint
Three hours after eating.....	0.144	Slight
Five hours after eating.....	0.114	Faint

One probable cause for the hyperglycemia was a fire drill in the forenoon, the acute panic and helplessness aroused by the gong being followed by great nervousness during most of the day. Possibly also the preceding fast tended to increase the hyperglycemia following carbohydrate ingestion. The patient was extremely desirous of visiting friends in New York, and as the indications were against diabetes, he was allowed to go on a short leave, in the hope that his nervous condition might be improved.

He returned November 1 much worse in his nervous condition from the excitement of the city. On a full mixed diet, moderate to heavy copper reduction tests were present in every urine voiding of every day. No blood samples were taken till the nervousness had abated somewhat. Then, November 5, the plasma sugar was 0.111 per cent. before breakfast, and November 8 it was 0.100 per cent. two hours after a carbohydrate rich breakfast. Also, November 5 a test was made with 25 gm. glucose in 150 c.c. solution, taken on an empty stomach in the morning.

TABLE 6.—PLASMA AND URINE SUGAR AS INFLUENCED BY GLUCOSE INGESTION

Time	Plasma Sugar, per Cent.	Urine	
		Volume, C.c.	Sugar
Before glucose .....	0.111	140	Slight
One hour after glucose.....	0.111	32	0.26 per cent.
Two hours after glucose.....	0.195	57	Moderate
Three hours after glucose.....	0.054	32	Faint

Beginning November 12, a trial was made of a low calory, carbohydrate-free diet as follows:

TABLE 7.—URINARY FINDINGS AFTER LOW CALORY CARBOHYDRATE FREE DIET

Date	Diet			Urine		
	Carbo- hydrate	Pro- tein	Calo- ries	Volume, C.c.	Sugar, Gm.	Nitroprussid Test
Nov. 12	0	80	589	1,000	Moderate	Faint
13	0	150	803	1,200	Slight	Faint
14	0	150	803	2,250	Faint	Faint
15	0	150	803	1,200	2.4	Faint
16	0	150	803	640	Heavy	Slight
17	0	150	803	650	1.14	Faint
18	0	150	803	610	0.34	Slight
19	0	150	803	400	0	Moderate
20	Full mixed diet, unweighed			925	13.32	Faint
21	Full mixed diet, unweighed			500	5.65	Negative
22	Full mixed diet, unweighed			1,150	8.1	Negative
23	Full mixed diet, unweighed			1,225	6.37	Negative
24	Full mixed diet, unweighed			1,150	8.81	Negative
25	Full mixed diet, unweighed			1,000	5.17	Negative
26	Full mixed diet, unweighed			750	4.1	Negative
27	Full mixed diet, unweighed			1,300	3.6	Negative
28	Full mixed diet, unweighed			975	4.23	Negative
29	Full mixed diet, unweighed			1,475	3.00	Negative
30	Full mixed diet, unweighed			Incomplete	0	Negative
Dec. 1	Full mixed diet, unweighed			1,450	Heavy	Negative
2	Full mixed diet, unweighed			Incomplete	Heavy	Negative
3	Full mixed diet, unweighed			600	Heavy	Negative

Two plasma sugar tests were taken during the period of carbohydrate free diet, between 9 and 10 a. m. in each instance (during digestion of breakfast). The result was 0.078 per cent. November 14, and 0.094 per cent. November 16. Sugar reactions were present in the urine for the periods represented by the blood samples—faint November 14, moderate to heavy November 16. There is thus some indication of a renal threshold. Throughout the period of observation, the urine was examined in at least four divisions in every twenty-four hours (according to the routine of the diabetic service). Sugar was constantly present, except on three occasions. One of these was the full day November 19, after a week of low calory carbohydrate free diet; another was November 30 on full mixed diet, the test covering not quite the entire day, one period being lost. The third time sugar was absent was a single specimen on another date, on which other specimens contained considerable sugar. On a mixed diet shortly before leaving the hospital, the plasma sugar was 0.096 per cent. January 8, and 0.080 per cent. January 11.

The urinary sugar regularly showed certain peculiarities. In the qualitative test with Benedict's copper reagent, the reduction was unusually slow in coming, and then often appeared much heavier than usual with slow tests. The character of the reduction was atypical, with a strong tendency to formation of the red or black oxids, so that this patient's test could generally be picked out at a glance from among the tubes of diabetic tests in the same rack. Titration with Benedict's

quantitative reagent indicated lower percentages than would have been expected from the final appearance of the qualitative tests, and the end point was always indistinct and sometimes impossible to find. On account of this difficulty, and the doubtful nature of the sugar, attempts at quantitative estimation were frequently omitted. Many fermentation tests were carried out with Fleischmann's yeast, with the invariable result of no gas formation, or only traces, and little or no change in the reducing properties, whereas glucose added to the same urine fermented promptly and apparently completely. As far as could be observed, these peculiarities remained the same on either a mixed or carbohydrate free diet.

Urine samples preserved with toluene, less than twenty-four hours old, were taken to Dr. P. A. Levene, being out of the ice-box only for about three hours on the trip from Lakewood to New York. He immediately observed the slow atypical reduction with Fehling's solution, and also performed tests which excluded the presence of pentoses, disaccharids, levulose and glycuronic acid. Circumstances then brought it about that the urine remained several weeks in the ice-box before further testing. Dr. Levene then performed osazone tests, and identified glucosazone by its crystals and melting point.

Other urine samples were similarly taken to Dr. Stanley R. Benedict, who found the sugar fermentable with yeast, and obtained a comparison of titration and polarimetric readings approximating the theoretical for glucose. He also prepared and identified glucosazone. (For other findings, see below.)

The patient's urine record in France was never obtained, but he stated that the reduction tests had frequently been negative there, and appeared or increased markedly with nervous attacks. His nervous and general condition rapidly improved in Lakewood with the aid of rest and physiotherapy, but the reducing properties of the urine persisted unchanged. When his recovery was almost complete, he was granted a thirty days' leave, which he spent at rest and quiet recreation in the country. He returned to the hospital free from all symptoms, except a slight nervousness of manner, and on his request he was discharged Jan. 22, 1919, to undertake quartermaster duty in New York. Notwithstanding the other improvement, the reduction test was positive in every specimen of urine the same as before.

Under the strain of work and excitement the patient broke down nervously, and was admitted to another military hospital. He improved more rapidly than before, was discharged from the army with no compensation for disability, and is now in civilian employment in New York. On advice, he reported several times to the laboratory of Dr. Benedict, who, with the fresh urine, found fermentation tests negative

or very incomplete, and other tests indicating a substance other than glucose. The problem of identification may be pursued further by Dr. Benedict, if circumstances permit.

CASE 3.—The wife of an army officer, American, aged 43 years, was admitted March 12, 1919.

*Family History.*—Her father died at 63 years of age from perforated gastric ulcer. Her mother is alive, but an invalid with rheumatism. One sister died when 18 months of age of unknown cause. One brother and three sisters are alive and well, though one of the sisters is obese. No inheritable disease is known in the family.

*Personal History.*—The patient had whooping cough, measles and chicken-pox in childhood, no other illness. She had two pregnancies, the first a premature birth with face presentation. There were no postpartum disturbances. She uses neither alcohol nor tobacco; has no excesses in food or sweets, but admits a tendency to become obese recently, so that she would like to reduce for the sake of both looks and comfort. She is not constipated. She spent two years in the Philippines when her husband was in campaign there; otherwise she has lived the usual army life in this country under good hygienic conditions. Her husband has been in France for the present war, and she has tried to be of service and also suppress worry by prolonged heavy work in relief organizations.

*Present Ailment.*—After the signing of the armistice, she experienced marked continuous lassitude, also slight pruritus and loss of weight. This led to a medical examination, which revealed glycosuria, and she came for treatment because of the diagnosis of diabetes rather than on account of any distressing symptoms.

*Physical Examination.*—She is 5 feet 9 inches tall and weighs 175 pounds. She has the appearance of perfect health and slight overweight. Her blood pressure is 125 systolic, and 75 diastolic. The examination was entirely negative, except for her heart. The heart was normal in size to physical and fluoroscopic examination, and its function was apparently normal, but there was a short systolic murmur in the aortic area, and electrocardiograms were interpreted to indicate a rotation of the organ to the right. Roentgenograms did not reveal any rotation.

*Laboratory Examination.*—The Wassermann was negative. A blood count was not made. The urine was normal to routine tests, except for sugar.

*Treatment and Progress.*—The patient was admitted on the afternoon of March 12, and was immediately started on the usual diabetic fasting program of soup, coffee and bran biscuits. Sugar freedom was attained March 13, the charted excretion of 0.83 gm. being only for the fore part of that day. When a carbohydrate tolerance test was attempted with green vegetables, a faint reducing reaction promptly returned and increased as the carbohydrate was increased. Table 9 gives the general record.

TABLE 8.—RENAL FUNCTION TESTS

	Blood Urea, Mg. per 100 C.c.	Phthalein Test	
		First Hour, per Cent.	Second Hour, per Cent.
Nov. 16.....	22.2		
Nov. 19.....	—	35	19

TABLE 9.—THE URINE AND BLOOD FINDINGS WITH VARIOUS DIETS IN CASE 3

Date 1919	Diet			Urine			Plasma Sugar, per Cent.	Remarks
	Carbo- hydrate, Gm.	Pro- tein, Gm.	Calo- ries	Volume, C.c.	Glucose, Gm.	Nitro- prussid Test		
Mar. 12	Admission			175	Heavy	Moderate		
13	Broth, bran, coffee			500	0.83	Heavy	0.100	Fasting blood sugar
14	25	8.6	154	775	Faint	Heavy	0.100	Fasting blood sugar
15	50	12.3	269	700	Slight	Heavy		
16	75	15.2	387	355	1.39	Heavy		
17	100	16.9	510	445	Moderate	Moderate	0.122	Blood 2 hours after noon meal
18	7.5	0	30	450	Very faint	Moderate		
19	General hospital diet from now on			875	7.00	Heavy		
20				800	11.58	Slight		
21				1,000	9.20	Negative		
22				825	Heavy	Negative		
23				800	Heavy	Negative		
24				1,025	Heavy	Negative	0.107	Blood 3 hours after breakfast
25				1,150	Heavy	Negative		
26				825	Heavy	Negative	0.117	Blood 3 hours after noon meal
27				1,250	Heavy	Negative		
28				375	Heavy	Negative	.....	Urine for only one period
29				975	Heavy	Negative		
30				.....	.....	.....	0.113	Blood 1½ hours after breakfast

TABLE 10.—RESULTS OF GLUCOSE TOLERANCE, PHENOLSULPHONEPHTHALEIN AND MOSENTHAL FIXATION TESTS IN CASE 3

Date	Time	Urine			Plasma Sugar, per Cent.	Remarks
		Volume, C.c.	Sugar, Gm.	Nitro- prussid Test		
Mar. 19	9:30 a.m.	125	Negative	Moderate	0.113	Fasting blood sugar. Given 100 gm. glucose in 200 c.c. of water
	10:30 a.m.	77	2.4	Faint	0.139	Drank 200 c.c. of water
	11:30 a.m.	143	3.6	Negative	0.125	Drank 200 c.c. of water
	12:30 p.m.	675	2.1	Negative	0.115	
Mar. 24	Phenolsulphonephthalein Test				Date	Blood Urea, Mg. per 100 C.c.
	First hour.....	35.6 per cent.				
	Second hour.....	28.2 per cent.			Mar. 17	18.62
	Total.....	63.8 per cent.			Mar. 30	15.77
Mosenthal Fixation Test						
Mar. 31	Time	Urine				Remarks
		Volume, C.c.	Sp. Gr.	NaCl, Gm.	NaCl, per Cent.	
	10 a.m.	190	1.028	2.21	1.16	Breakfast, 8 a.m.; dinner, 12 noon; supper, 5:30 p.m.
	12 noon	100	1.030	1.56	1.56	
	2 p.m.	102	1.035	1.39	1.36	
	4 p.m.	200	1.030	2.88	1.44	
	6 p.m.	88	1.035	1.35	1.54	
	8 p.m.	112	1.034	1.50	1.34	
	Night	380	1.034	4.10	1.08	
		1,172		14.99		

## GENERAL DISCUSSION

A review of the literature is omitted, because it has been covered by several recent authors, and also because the facts do not yet afford a simple or harmonious conception of the condition. Certain deductions in connection with the present group of three cases suggest themselves as follows.

## 1. INCIDENCE

As the most important characteristic of this anomaly is the excretion of glucose or a glucoselike substance with a normal or low level of blood sugar, the introduction of simple methods of blood sugar analysis within the past few years has permitted a more extensive and accurate investigation than was possible before. The considerable number of wholly or partially demonstrated cases reported in this time has established firmly the existence of such a condition, and has also indicated that it is not actually a rarity. The proportion of three "renal" cases to thirty-seven of true diabetes in this hospital is surprisingly and perhaps exceptionally high, but interesting in view of the random selection of patients, who were simply those soldiers in whom some military officer happened to diagnose glycosuria. The odds were thus strongly in favor of true diabetes, because young diabetics ordinarily show symptoms leading sooner or later to the diagnosis, while the vast majority of enlisted men never had a urine examination at any time, and because of the absence of symptoms the "renal" cases could be discovered only in that small minority who were subjected to urinalysis for some other cause. Doubtless some of the examples of atypical or "harmless" diabetes which formerly puzzled clinicians were actually "renal" in character, and the recognition of this group will reduce the number of diabetic cases in which it is imagined that diet may be neglected with impunity. Life insurance statistics furnish the best evidence against the existence of abnormal glycoresis in any high percentage of the population, but they are imperfect because of the usual lack of blood analyses; the latter may sometimes be necessary for this purpose in the future. It is of some interest for comparison that no cases of levulose, pentose or glycuronic acid excretion were found in this service.

## 2. ETIOLOGY

*A. General Physical Condition.*—No constant relation was discoverable between the urinary anomaly and anything in the physical examination of the patients. Patient No. 1 had a remarkable cardiac disturbance, which appeared serious in examination, but had never caused subjective symptoms. Patient No. 3 had the suggestion of a slight cardiac rotation, according to electrocardiographic examination.

But the heart and circulation of patient No. 2 were normal, unless the nervous shock was responsible for some functional change not revealed by examination. Otherwise all three patients appeared to be in very good physical condition. Patient No. 1 had been slightly, and patient No. 2 more seriously exposed to mustard gas, but the woman, patient No. 3, had remained safe in this country.

*B. Nervous System.*—Patient No. 2, when first admitted, seemed to furnish something which had been awaited with curiosity throughout the whole duration of the diabetic service, namely, a case of diabetes due to war injury. There was a history of repeated urine examinations showing absence of glycosuria up to induction into service, then a tremendous shock and trauma, followed by persistent sugar excretion. But this, the only traumatic case seen, turned out to be of the “renal” type, and it thus appears as though this condition here had been caused by traumatism and nervous shock. Such an occurrence, if positive, is important as the only known example of definite causation of this anomaly by this or any other means, for certain cases in the literature seem to have been congenital, but in the great majority the time and mode of origin have been entirely unknown. Patient No. 3 in the present series had had some worry and strain, but patient No. 1 was a happy-go-lucky individual, who had suffered no shock or important injury, and was the reverse of neurotic in nature. There is no information whether the urinary condition in these two patients was congenital, or as to the time or cause if it was acquired.

*C. Kidneys.*—The first writers on this condition regarded it as associated with nephritis, and thus seemingly on a par with the occasional glycosuria in animals poisoned with uranium, chromium, etc. The more recently reported cases, including the great majority and the ones most thoroughly studied, have been independent of albuminuria or known renal lesions, past or present. But the name “renal glycosuria” still carries with it the assumption that the seat of the anomaly is in the kidney. None of the three patients in this series had albumin, casts or blood in the urine, or gave any history of nephritis, unless the kidneys of two of them might have been irritated by mustard gas. The blood urea was slightly elevated in patient No. 1, normal in the other two. The index of urea excretion was normal in all three, and the Mosenthal fixation test was normal in the only one (No. 3) in whom this test was made. On the other hand, the phenolsulphonephthalein elimination of all three of these patients was slightly low. The phenolsulphonephthalein tests were carried out in the general laboratory of the hospital, by the same workers and with the same technic as all the tests of this sort in the hospital. The poor phenolsulphonephthalein function of these three patients may, perhaps, be only

a peculiar coincidence, but suggests the desirability of similar tests in other cases of this kind. It may be worth while also to call attention to the entire lack of necropsies in such cases, and the interest attaching to any that may be obtainable, for questions not only of ordinary renal pathology, but also (if the glycosuria continues to death) of the Armanni or Ehrlich vacuolation and glycogenic infiltration which is a regular feature of severe diabetes and phloridzin glycosuria.

### 3. PROGNOSIS

In certain instances in the literature the continuance of "renal glycosuria" for many years has been proved, and apparently no case has ever been described in which it is known to have ceased. On the other hand, it is reckoned as harmless, and no known injury has resulted from it in any reported case. Even in the few cases of greatest severity in the literature, in which the sugar excretion has been so great as to be comparable to true diabetes and to cause danger of acidosis when carbohydrate was restricted, it was only necessary for the patient to take a sufficiently liberal carbohydrate diet to be free from all disagreeable symptoms, except sometimes polyuria. This condition thus furnishes interesting evidence that the weakness and other disturbances of health in true diabetes are not due solely to the loss of sugar from the body. The importance of a clear distinction in definition between diabetes and glycosuria (or glycuressis—Benedict) is also thus emphasized. The observations in the present three cases conform to the foregoing statements concerning the prognosis.

### 4. URINE VOLUME

As mentioned, polyuria has characterized some cases in the literature, particularly when the sugar output was large. Inspection of the tables for these three patients shows that there was never an excessive urinary volume, but sometimes, on the contrary, a marked oliguria. There was never any appreciable fluid retention, and the elimination was proportionate to the intake, the patients merely saying that they had no desire to drink. This behavior is not altogether exceptional, as the sugar excretion, on the whole, was rather low, and it is well known that in certain cases of true diabetes the urine volume for some reason fails to show the usual increase. In a few glucose tolerance tests, however, the fluid relations observed were of some interest. Patient No. 3, for example, receiving 100 gm. glucose March 19, had considerable sugar percentages in the urine, but the urine volume was in inverse relation, the marked polyuria of 675 c.c. in the third hour coinciding with the lowest percentage of reducing substance. The peculiarities of diuresis in the tolerance tests of patient

No. 1 were mentioned in the description of that case. The influence of hyperglycemia seemed to be opposite in the two cases. There might be a chance of instructive comparisons of the urine volume in true diabetes with hyperglycemia, and that in "renal" cases with, perhaps, equal glycosuria and either elevated or normal blood sugar, except for our ignorance of the mechanism and even of the exact nature of the reducing substance in the latter cases. The one general conclusion which can be drawn from all three of the present cases is that the sugar excretion and the water excretion, on the whole, behave as separate functions. Increase of sugar does not necessarily increase the urine volume, and increased water elimination has no appreciable influence in sweeping out an additional quantity of sugar.

## 5. METABOLISM

*A. Fat Metabolism.*—On the whole, especially in Patients No. 1 and 2, acetonuria was conspicuous by its absence. It was present sometimes with fasting or restricted diet, but only to the extent of slight or moderate urinary reactions; a positive nitroprusside test in the blood plasma or lowering of the  $\text{CO}_2$  capacity was never observed, and also no subjective symptoms. Acetonuria was distinctly more prompt and marked in Patient No. 3, but the difference is readily explainable by her slight obesity. Differences of this order are the familiar experience with both normal persons and patients with true diabetes. In none of the three cases of this series was there any sign of unusual tendency to acidosis, either as a specific phenomenon or in consequence of the loss of sugar.

A few estimations of blood lipoids were performed in Case 1 on the chance of detecting any abnormalities; but though the lecithin values were high, and the absence of digestive hyperlipemia seemed comparable with the absence of hyperglycemia after carbohydrate, no general conclusions can be drawn from this single experiment.

*B. Protein Metabolism.*—As already described under Case 1, a meal of bacon and eggs, eaten when glycosuria was absent, following the glucose tolerance test of December 12, brought about the elimination of 1 gm. sugar during the night. The experiments with beef-steak on January 16 and 17 showed that protein could give rise to slight glycosuria with or without elevation of the blood sugar. It is well known that phloridzin glycosuria is increased by protein feeding, and the sugar excretion is supposedly independent of the blood sugar level. The observations in Case 1 suggest some resemblance to the phloridzin process in this respect.

*C. Carbohydrate Metabolism.*—Certain salient features common to these three cases and to most or all of the genuine cases in the litera-

ture may be summarized as follows: (1) A tendency to glycosuria so strong that sugar freedom is possible only with stringent restriction of diet or actual fasting, to such a degree that health would be seriously impaired by attempting to keep glycosuria absent, if, indeed, life were possible at all—the cases in this respect surpassing true diabetes, except for very rare examples of extreme severity; (2) normal power of actual carbohydrate utilization, as manifested by “paradoxical tolerance”; i. e., though some process in the kidney or elsewhere causes the waste of a certain quantity of carbohydrate, and this quantity may increase with increased carbohydrate ingestion, yet the soundness of the fundamental assimilative function is shown by the ready utilization of the greater part of every starch or sugar intake, no matter how large; (3) though the blood sugar level is subject to some variations, the low values found in many cases even after large starch or sugar ingestion stand in contrast not only to the conditions in diabetes, but also to the hyperglycemia of normal persons after such feeding. The supposition that the kidneys here merely perform, more efficiently than in normal persons, the function of keeping the blood sugar concentration normal, encounters the following difficulties: First, the quantity excreted is often so small compared with the quantity ingested that the suppression of hyperglycemia through this drain alone seems questionable; second, the sugar curve does not necessarily correspond to the severity of the case or the intensity of the excretory process; the blood sugar may run low when the sugar loss is trivial, or higher when the excretion is considerable; third, there are other discrepancies, such as found in the protein test of Patient No. 1 on January 17. Here glycosuria was slight; not only did the kidneys fail to react so as to keep the blood sugar normal, but it was actually higher than should be expected in a normal person under the circumstances.

*D. Total Metabolism.*—There was some curiosity whether the sugar excretion was influenced only by the carbohydrate or by the total calories of the diet, but the observations on this point were very incomplete. No tests were performed with feeding of pure fat or alcohol. The details with various diets were mentioned in the description of Case 1. Patient No. 2, because of his nervous condition, was never subjected to fasting, but on a carbohydrate-free diet of 150 gm. protein and 800 calories the glycosuria fell to the vanishing point and possibly would have remained absent, the liberal protein alone failing to maintain the glycosuria. The only information from Case 3 is that glycosuria ceased very easily with fasting and returned with the feeding of only 25 gm. carbohydrate in green vegetables. It is a safe general conclusion that “renal glycosuria” is influenced chiefly by the pre-

formed carbohydrate and in smaller degree by the protein of the diet; but the evidence in Case 1 indicates, as far as it goes, that there is little or no influence of the total calories apart from these direct sources of carbohydrate.

Determinations of the respiratory metabolism may offer something of interest not only in general, but particularly in regard to the carbohydrate economy. They may show whether the rate of combustion of ingested carbohydrate is normal, and this again may throw some light on the rôle of mass action in assimilation. It seems to be a general law that when the concentration of any food substance is increased in the blood, both the combustion and the storage of that substance are increased, but there seem to be obstacles to considering the latter increase as caused by the former through simple mass action. Therefore, the possible demonstration of a rise of carbohydrate metabolism due to carbohydrate ingestion without the usual rise of blood sugar may be instructive, though there is an additional possibility that occult forms of carbohydrate in the blood may require consideration as well as the ordinary sugar.

#### 6. CHARACTER OF THE SUBSTANCE EXCRETED

For convenience and brevity, the terms "glycosuria," "glucose" and "sugar" have been used with reference to the reducing substance in the urine, but are not intended for strict interpretation. In Case 2 the absence of fermentation with yeast created suspicion of pentosuria, which was excluded by the tests of Drs. Levene and Benedict. Subsequently, Benedict demonstrated that the reducing substance in this case was neither glucose nor any of the sugars heretofore reported in urine, but a new substance of yet unknown nature. In Cases 1 and 3 the reactions observed were typical for glucose, but in a strict sense glucose excretion was not positively demonstrated in these or in any cases in the literature. Case 2 may be exceptional, but the difficulty with fermentation in Case 1 on a few occasions suggests the possibility of transitions or close relations as respects the excreted substance. Absolute demonstration of glycosuria must consist of two parts; first, strict proof that the substance found in analysis is glucose; second, proof that this substance is present in urine obtained as fresh from the kidney as possible, and is not the product of changes occurring during standing or manipulation or even in the bladder.

#### 7. NATURE OF THE CONDITION

Such scattering suggestions as the observations offered concerning the seat or nature of the anomaly are contained in the above summary. The hypothesis of E. Frank, that the apparently normal blood sugar

is due to impermeability of the corpuscles and the basis of glycosuria is a high level of sugar in the plasma, is here excluded because all the analyses were performed upon plasma. It had been planned to present a series of parallel plasma and whole blood analyses to show the permeability of the corpuscles, both for this reason and also as a matter of possible interest in comparison with the apparently increased permeability of the kidneys for sugar, but it was found at the end that the whole blood determinations had been invalidated by a slight technical error. The proportion of plasma and corpuscles as indicated by centrifugation in a graduated tube was followed as a routine in the laboratory; the results, being normal, are omitted, but as far as this method is concerned no connection was shown between this form of mellituria and the blood volume in Epstein's sense. A similarity to the phloridzin process is often suggested, but until something definite is learned concerning the actual mechanism in one or the other, the comparison of unknown with unknown must remain unproved and unprofitable. It is difficult to bring all cases in the literature under the same general rules, and uncertain whether they represent merely degrees and variations of one fundamental condition (confused sometimes with mild diabetes, or possibly sometimes complicated by it), or whether further study will reveal a group of independent anomalies. Benedict's recent investigation<sup>2</sup> includes one case which must be classified under the existing nomenclature as "alimentary renal glycosuria," provided it is not diabetes. The general information derived from Benedict's new methods is that all urine contains traces of carbohydrate in varying kinds and quantities, and that marked differences exist between individuals. The anomaly in question may prove to be only an unusual exaggeration of this normal process; it is conceivable that all gradations may be found between the strictest normality and the most extreme "renal glycosuria" with regard to the excretion of fermentable and unfermentable carbohydrate. Some facts, such as the peculiar blood sugar curves following carbohydrate or protein ingestion, do not fit easily with this supposition, but at present it promises nevertheless to be the most fruitful field for research.

#### SUMMARY AND CONCLUSIONS

1. The observation of three of these cases, as compared with thirty-seven cases of true diabetes in military service, and the increasing number of reports in the literature as blood sugar analyses are more employed, indicate that "renal" glycosuria is not as rare as once supposed, and probably is much commoner than other anomalies such as pentosuria or levulosuria.

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2. J. Biol. Chem. **34**:195 (April) 1918.

2. The etiology, whether congenital or acquired, is unknown in two of these three cases. The history in one case is of special interest, as suggesting that severe trauma was either the primary or at least the exciting cause.

3. There was no indication of nephritis or renal abnormality in any of the three cases, except a slightly subnormal phenolsulphone-phthalein elimination.

4. The apparent absence of harm in all three patients on unrestricted diet with continuous sugar excretion agrees with the favorable prognosis of this condition according to the literature. The only disturbance of health is that resulting from the severe restrictions of diet necessitated by any attempt to stop the sugar excretion. The sharp contrast with true diabetes in this respect is of theoretical as well as practical interest.

5. No fixed relations were observed between the sugar in blood and urine. The renal excretion does not necessarily serve to maintain a low level of blood sugar. The output is not always higher with high than with low blood sugar.

6. No fixed relations were observed between sugar and water elimination, in the sense either of polyuria due to glycosuria, or a flushing out of extra sugar by increased diuresis. More detailed studies of this and the preceding point would be desirable.

7. The sugar excretion seems to be determined by the supply of available carbohydrate, especially preformed, but also to less degree by the potential carbohydrate of protein. The fat ration and total metabolism, which are important in true diabetes, are probably without influence here.

8. Analyses of blood fat in one case showed abnormalities from which no conclusion can be drawn. No abnormal tendency to acidosis was observable in any of the three cases.

9. The excreted substance in one of the three cases seemed to be an unknown sugar, distinguished from glucose by the absence or incompleteness of fermentation. This may be the most important observation of the present study, and suggests the desirability of closer examination of the fresh urine in such cases for accurate identification of the sugar.

10. The nature of so-called "renal glycosuria" is not established. Frank's hypothesis of a high plasma sugar did not hold in these three cases. It is not yet proved that the abnormality lies in the kidney, or that it consists merely in a lowering of the normal threshold of sugar excretion. It is possible that cases differ in kind as well as degree, and that a group of anomalies have heretofore been included under this name.

# A GROUP OF SIXTY-EIGHT CASES OF TYPE I PNEUMONIA OCCURRING IN THIRTY DAYS AT CAMP UPTON

WITH SPECIAL REFERENCE TO SERUM TREATMENT

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From February 10, to March 12, 1919, 135 cases of pneumonia were admitted to the Base Hospital; of this number, 50 per cent., or sixty-eight cases, were diagnosed bacteriologically as having type I pneumococcus the predominating organism in their infection.

This small epidemic was practically confined to colored troops, only four out of the sixty-eight cases affecting white men. These troops embarked from Brest, sailing to New York, and were then transferred to Camp Upton for demobilization.

On entering the hospital they presented the picture of acute lobar pneumonia. The classical signs were present in all, and only differed in the intensity of their symptoms. Starting with a chill — pain in the affected side, grunting respiration, with dilating alae nasi completed the picture of this type of disease. The early sputum was blood streaked; later it became prune juice in color. Dulness over the affected area became an early sign, and this was associated with bronchial and tubular breathing which increased with intensity as the dulness increased. The vocal fremitus was marked and we soon saw that we were dealing with acute lobar pneumonia.

There had been only eighteen cases of type I pneumonia during the influenza epidemic, and this group of cases was considered a fertile field for a thorough test of the type I serum as a method of treatment. Over 90 per cent. of these cases presented the picture of healthy seasoned troops, and it was with much interest that we watched the outcome of this method of treatment originated by the Rockefeller Institute and so admirably portrayed in their monograph dated October 16, 1917. We have used this method of treatment in our other cases of type I pneumonia, but they were not many and were distributed more or less irregularly throughout the different seasons of the year.

In the sputum typing of these cases, fifty-eight were straight type I, while ten were mixed; but with type I pneumococcus predominating, and were not different in any detail from the type ones.

In the table we have listed these cases by number, trying to arrange them as nearly as possible on the day and hour of their admission. Their date of embarkation and debarkation with the date of arrival and probable date of the onset of their sickness. The date of their arrival at the hospital, with the date of the typing of the sputum, corresponds to the date with the hour mentioned of the first injection of the serum. The table also shows the total amount of serum at eight-hour intervals given to each patient; the temperature, pulse and respiration on admission; the lobes of the lungs clinically involved, represented in numbers corresponding to number 1 the right upper; number 2, the right middle; number 3, the right lower; number 4, the left upper, and number 5, the left lower. A blood count was taken in nearly all of the cases and evidenced a marked leukocytosis with a high polymorphonuclear count, which is characteristic in this condition. The urine showed albumin and casts. In the majority of cases, 1 plus, corresponding to a trace, up to 3 plus, which is a marked amount. The casts are recorded in like manner, and these findings well represent the condition of the urine found in this type of pneumonia. The roentgen ray was used in checking up the clinical findings and the lobes involved are also represented numerically. Blood cultures were taken as indicated. We have tried to classify the recovered cases under the headings of crisis and lysis, and we have used in our distinction for crisis any temperature which drops to normal within thirty-six hours. The disposition of the case is determined by either duty or death, with the date corresponding in each column. Under remarks we have mentioned the principal complications which were characteristic of this group of cases, or we call attention to any abnormality which arose. The necropsy remarks are limited to the chest findings with the exception of two cases, one associated with pericarditis with effusion and the other with meningitis.

On admission to the pneumonia wards the physical examination was at once made, and if lobar pneumonia was present or suspected the patient received  $\frac{1}{2}$  c.c. of normal horse serum subcutaneously for desensitizing purposes; at the same time, the sputum was sent to the laboratory for typing. This method saved about five hours, the time which must elapse after giving the horse serum before the antipneumococcic serum may be administered. During this time, while waiting for the typing to return, a blood count is made and in many cases a blood culture is taken. The urine was sent for examination and a roentgen-ray examination was ordered to check the physical findings.

Within from four to six hours after the patient's admission to the hospital he is ready to receive his first injection, and we have obtained enough physical and laboratory data for accurate interpretation, before any change which might take place after the administration of the first dose of serum. We were also able to satisfy ourselves that after giving the first injection, there was little change in the blood picture. For example, we found that a differential count made before and shortly after the serum was administered remains the same. Only three cases of slight anaphylaxis occurred; a few had a thermal reaction immediately following the injection, similar in character to the reaction following the injection of a foreign protein intravenously, this being followed by a chill, elevation of temperature and sweating. This reaction has always been a favorable one in our experience and several times has resulted in prompt recovery by crisis. The serum sickness came on in practically all of the cases in from four to sixteen days after the last injection, the greatest discomfort being from the urticaria and occasionally from asthma. These symptoms were readily relieved by a hypodermic injection of from  $\frac{1}{2}$  to 1 c.c. of epinephrin in a 1:1,000 solution. The serum was given at eight-hour intervals, day and night, until the rectal temperature registered 100 or lower, or evidence of complications of impending death made it advisable to stop the treatment.

The dosage employed was 100 c.c. given intravenously, keeping the serum slightly warmer than the body temperature and allowing it to flow in very slowly. A gravity bottle was used, this being connected with an intravenous needle by rubber tubing around which were wrapped warm towels, to keep the solution at the proper temperature. A feeling of warmth was mentioned by many of the patients and sweating was common during the administration. Many of them complained of itching over different parts of the body and a few had manifest symptoms of urticaria, and it was the marked exception for an attack of asthma to come on during the administration of the initial dose. We have used any one of the three different preparations of the serum we have had in stock and frequently patients would, during their course of treatment, have serum from all three kinds. We have demonstrated to our own satisfaction that the serum does no harm.

Sixty-one of the sixty-eight patients received the serum; the least amount given to any one individual was 30 c.c., the largest amount, 900 c.c. The total amount used was 20,955 c.c., or the average amount per patient of 344 c.c. Of the seven not receiving serum, six were in convalescence when typed and one received no serum because of the diagnosis of type 4 pneumococcus and *Bacillus influenzae* in the sputum, but at necropsy this case showed a pure culture of type I pneumococcus from the heart's blood.

## CONDENSED REPORT OF THE FINDINGS OF—

Case No.	Date of Embarkation	Date of Debarcation	Date of Arrival at Upton	Date of Onset of Disease	Date of Admission to Hospital	Date of Typing of Sputum	Hour of First Serum Injection	Total Amount Given, C.c.	On Admission			Lobes Involved 1-2-3-4-5 Number of Lobe	Blood Count	
									Temperature	Pulse	Respiration		W.B.C.	Poly.
1	2/ 2/19	2/10/19	2/10/19	2/ 7/19	2/10/19	2/11/19	10:30 p.m.	300	102.2	136	36	3	28,600	94
2	2/ 2/19	2/10/19	2/10/19	2/ 6/19	2/10/19	2/11/19	11:00 a.m.	300	105.4	124	30	4-5	21,800	82
3	2/ 2/19	2/10/19	2/10/19	2/ 9/19	2/10/19	2/11/19	10:00 p.m.	500	105.2	104	28	2-3	15,600	86
4	2/ 1/19	2/ 9/19	2/10/19	2/11/19	2/12/19	2/16/19	2:15 p.m.	500	103.2	88	22	5	12,200	79
5	2/ 4/19	2/12/19	2/12/19	2/ 8/19	2/12/19	2/13/19	8:30 p.m.	300	102.4	112	46	5	42,200	91
6	2/ 1/19	2/ 9/19	2/10/19	2/ 9/19	2/12/19	2/13/19	12:30 p.m.	30	100	80	20	4	.....	..
7	2/ 4/19	2/12/19	2/12/19	2/ 8/19	2/12/19	2/13/19	.....	...	101.6	96	22	2	13,400	75
8	2/ 2/19	2/10/19	2/10/19	2/12/19	2/13/19	2/13/19	1:30 p.m.	100	101.6	112	36	1-2	27,000	80
9	2/ 1/19	2/ 9/19	2/10/19	2/ 9/19	2/13/19	2/16/19	3:00 p.m.	100	103.2	100	24	1 3	6,600	71
10	Camp organization			2/12/19	2/13/19	2/21/19	10:30 a.m.	100	102	100	28	3 5	5,400	58
11	2/ 1/19	2/ 9/19	2/10/19	2/10/19	2/14/19	2/16/19	8:30 p.m.	100	102	120	28	3	17,600	90
12	2/ 4/19	2/12/19	2/12/19	2/13/19	2/15/19	2/17/19	8:00 p.m.	200	105.2	114	32	4-5	25,600	81
13	2/ 4/19	2/12/19	2/12/19	?	2/15/19	2/16/19	12:00 a.m.	200	103	110	40	1-2-3	20,100	83
14	2/ 2/19	2/10/19	2/10/19	2/12/19	2/16/19	2/18/19	8:00 p.m.	200	101.4	104	36	1-2-3	20,100	83
15	2/ 3/19	2/11/19	2/12/19	2/16/19	2/16/19	2/18/19	8:00 p.m.	400	104	118	28	5	27,300	80
16	2/ 3/19	2/11/19	2/12/19	2/17/19	2/17/19	2/18/19	10:30 p.m.	400	103.2	108	24	5	25,000	89
17	2/ 1/19	2/ 9/19	2/10/19	2/16/19	2/17/19	2/19/19	10:30 p.m.	185	103.8	120	30	1-2	28,000	85
18	2/ 2/19	2/10/19	2/10/19	2/17/19	2/18/19	2/23/19	10:00 p.m.	600	101	96	22	1	.....	..
19	2/ 4/19	2/12/19	2/12/19	2/18/19	2/19/19	2/24/19	12:00 a.m.	500	98	100	18	4-5	.....	..
20	2/ 3/19	2/11/19	2/12/19	2/ 8/19	2/16/19	2/18/19	.....	...	100	112	28	1 3	.....	..
21	Camp organization			2/20/19	2/21/19	2/23/19	.....	...	103	115	30	5	.....	..
22	2/ 2/19	2/10/19	2/10/19	2/21/19	2/22/19	2/24/19	12:00 a.m.	400	104	120	24	4-5	27,500	?
23	2/16/19	2/24/19	2/24/19	2/25/19	2/26/19	2/27/19	8:00 p.m.	200	103.4	120	36	5	.....	..
24	2/16/19	2/24/19	2/24/19	2/16/19	2/28/19	3/ 1/19	11:30 p.m.	300	102	100	28	1-2-3	.....	..
25	2/16/19	2/24/19	2/24/19	2/27/19	3/ 3/19	3/ 4/19	.....	...	105.6	112	32	5	.....	..
26	2/23/19	3/ 1/19	3/ 2/19	3/ 3/19	3/ 4/19	3/ 6/19	4:00 p.m.	100	105.8	126	46	3	.....	..
27	2/23/19	3/ 1/19	3/ 2/19	2/25/19	3/ 5/19	3/ 6/19	8:00 p.m.	400	102	108	36	1-2	17,000	78
28	2/ 3/19	2/11/19	2/11/19	2/10/19	2/11/19	2/13/19	7:30 p.m.	100	102.8	102	24	1-2-3-4	16,700	..
29	2/ 2/19	2/10/19	2/10/19	2/11/19	2/12/19	2/13/19	8:15 p.m.	385	105	126	36	5	59,000	23
30	2/ 1/19	2/ 9/19	2/10/19	2/12/19	2/14/19	2/16/19	8:00 p.m.	200	103.3	118	36	5	18,200	86
31	2/10/19	2/10/19	2/10/19	2/12/19	2/15/19	2/18/19	11:20 p.m.	100	104	120	30	1	21,000	87
32	2/ 3/19	2/11/19	2/12/19	2/ 9/19	2/16/19	2/18/19	8:00 p.m.	500	103.8	120	30	3	28,000	85
33	2/ 3/19	2/11/19	2/12/19	2/16/19	2/17/19	2/18/19	11:00 p.m.	400	104.4	118	30	1	21,600	91
34	2/ 2/19	2/10/19	2/10/19	2/14/19	2/18/19	2/21/19	4:15 p.m.	200	104.6	116	34	2-3	7,700	..
35	2/ 2/19	2/10/19	2/10/19	2/15/19	2/19/19	2/21/19	8:00 a.m.	200	101.8	92	26	5	9,600	61
36	2/16/19	2/24/19	2/24/19	2/23/19	2/27/19	3/ 3/19	2:00 p.m.	400	103	100	40	3	.....	..
37	2/16/19	2/24/19	2/24/19	2/25/19	2/27/19	2/28/19	12:00 p.m.	400	104	104	36	3	.....	..
38	2/20/19	2/28/19	2/28/19	2/28/19	2/28/19	3/ 3/19	10:30 p.m.	400	103	106	24	5	.....	..

## —SIXTY-EIGHT CASES OF TYPE I PNEUMONIA

Urine		Roentgen-Ray Findings Lobes 1-2-3-4-5 Number of Lobe	Blood Culture	Date of		Date of		Remarks: Complications and Necropsy Findings
Albumin	Casts			Crisis	Lysis	Duty	Death	
2 plus	Neg.	1-2	Not taken	Temp. 103.6 at death		.....	2/15/19	Marked delirium throughout, marked toxemia Necropsy—Right pleural cavity, 100 c.c. turbid fluid; fibrinous exudate on surface of 1 and 2; 1, 2, 3 gray hepatization
2 plus	Neg.	5 fluid left base	.....	Temp. 99.6 at death		.....	2/18/19	Marked delirium throughout, marked toxemia Necropsy—Lobes 4, 5 covered with yellow exudate, consol. throughout containing no air; 1, 2, 3 bronchopneumonia
1 plus	Neg.	2-3	.....	.....	2/12 to 2/17/19	3/12/19	.....	None
Neg.	Neg.	.....	.....	.....	2/15 to 2/19/19	3/14/19	.....	None
2 plus	2 plus	4-5 fluid left base	.....	Temp. 99.2 at death		.....	3/10/19	Empyema, acute pericarditis Necropsy—Left pleura, 1,000 c.c. thick yellow pus; acute pericarditis; 500 c.c. of turbid fluid in pericardium
Neg.	Neg.	.....	.....	2/14/19	.....	2/27/19	.....	Anaphylaxis
1 plus	Neg.	.....	.....	2/13/19	.....	2/27/19	.....	Temperature never over 100.2
1 plus	Neg.	.....	.....	2/15/19	.....	3/ 1/19	.....	Atypical crisis
1 plus	Neg.	.....	.....	2/15/19	.....	3/ 4/19	.....	Leukocyte count after normal temperature
1 plus	Neg.	.....	.....	2/23/19	.....	3/12/19	.....	Leukocyte count after normal temperature
1 plus	Neg.	3-thickened pleura rt. base	.....	2/16/19	.....	3/18/19	.....	Atypical crisis
Neg.	Neg.	.....	Sterile	Temp. 103 at death		.....	2/19/19	Marked toxemia, beginning empyema rt. side Necropsy—Lobes 4 and 5, fibrinous exudate, firmly consolidated throughout
1 plus	Neg.	.....	Positive for Type I	Temp. 103.6 at death		.....	2/19/19	Admitted in convulsions Type I pn. meningitis Necropsy—1, 2, 3 firmly consolidated; meningitis Type I pneumococcus
2 plus	Neg.	.....	Sterile	2/18/19	.....	3/ 2/19	.....	
1 plus	Neg.	Sterile	.....	2/17/19	.....	3/12/19	.....	
1 plus	Neg.	.....	.....	2/19/19	.....	3/12/19	.....	Pseudo crisis and post-critical rise, 12 hours Ending by crisis on second day, serum sickness marked
1 plus	Neg.	1-2	.....	.....	2/17 to 3/22/19	3/ 4/19	.....	
Neg.	Neg.	1-2	.....	2/24/19	.....	3/14/19	.....	Atypical crisis
1 plus	1 plus	4-5 thickened pleura and fluid	.....	.....	2/24 to 2/26/19	3/14/19	.....	
Neg.	Neg.	.....	.....	2/18/19	.....	3/ 6/19	.....	Crisis on same day as typing, no serum
Neg.	Neg.	.....	.....	.....	2/21 to 2/24/19	3/14/19	.....	Lysis began on day of admission
1 plus	1 plus	4-5 thickened pleura	.....	2/28/19	.....	3/14/19	.....	Pseudo crisis followed by crisis
Neg.	Neg.	.....	.....	3/ 2/19	.....	3/14/19	.....	
Neg.	Neg.	1-2-3	.....	.....	3/2 to 3/ 5/19	3/21/19	.....	
1 plus	1 plus	.....	.....	3/ 5/19	.....	3/21/19	.....	Crisis occurred on day of admission, no serum
1 plus	1 plus	.....	.....	3/ 6/19	.....	4/15/19	.....	Single dose of serum given during crisis
1 plus	1 plus	1-2	.....	.....	3/6 to 3/10/19	3/14/19	.....	Secondary rise of temperature not due to serum sickness
Neg.	Neg.	1-2-3-4	.....	.....	2/15 to 2/17/19	4/15/19	.....	Delayed resolution with irregular temperature
1 plus	2 plus	5 fluid at base	.....	2/15/19	.....	4/ 1/19	.....	Serum reaction severe
Neg.	Neg.	Lungs neg. for fluid	Sterile	2/18/19	.....	3/ 22/19	.....	
Neg.	Neg.	e-3	Sterile	.....	2/17 to 2/22/19	3/21/19	.....	Cause undetermined, prolonged lysis
Neg.	Neg.	1-2	.....	.....	2/20 to 2/26/19	4/ 5/19	.....	
Neg.	Neg.	1	.....	2/28/19	.....	3/19/19	.....	Moderate jaundice, delayed resolution
2 plus	2 plus	1-2	Sterile	.....	3/4 to 3/7/19	3/22/19	.....	
1 plus	1 plus	5	.....	2/21/19	.....	4/ 5/19	.....	Delayed crisis
Neg.	Neg.	2-3	.....	3/ 4/19	.....	3/21/19	.....	Negative
1 plus	2 plus	2	.....	.....	3/2 to 3/5/19	3/28/19	.....	Delirium
1 plus	1 plus	.....	.....	3/ 4/19	.....	3/21/19	.....	

## CONDENSED REPORT OF THE FINDINGS OF SIXTY-EIGHT—

Case No.	Date of Embar-kation	Date of Debar-kation	Date of Arrival at Upton	Date of Onset of Disease	Date of Admis-sion to Hos-pital	Date of Typing of Sputum	Hour of First Serum Injection	Total Amount Given, C.c.	On Admission			Lobes Involved 1-2-3-4-5 Number of Lobe	Blood Count	
									Tempera-ture	Pulse	Respira-tion		W.B.C.	Hoby.
39	2/16/19	2/24/19	2/24/19	2/24/19	2/26/19	2/28/19	8:15 p.m.	250	105.2	112	32	1-2	.....	..
40	2/10/19	2/28/19	2/28/19	3/ 6/19	2/ 8/19	3/ 9/19	10:00 p.m.	300	100	90	22	1-2	7,000	62
41	2/25/19	3/ 5/19	3/ 6/19	3/ 7/19	3/ 8/19	3/ 9/19	10:00 a.m.	500	102.4	100	20	3	8,000	52
42	2/23/19	3/ 1/19	3/ 2/19	3/ 1/19	3/ 2/19	3/ 4/19	12:00 p.m.	300	102	110	20	4-5	.....	..
43	2/26/19	3/ 6/19	3/ 6/19	3/ 2/19	3/ 6/19	3/ 7/19	12:00 p.m.	300	105.2	118	30	4	16,000	77
44	2/23/19	3/ 1/19	3/ 1/19	3/ 3/19	3/ 5/19	3/ 7/19	12:00 p.m.	100	101	114	32	5	.....	..
45	2/23/19	3/ 1/19	3/ 1/19	3/ 6/19	3/ 6/19	3/ 8/19	12:15 p.m.	600	104.4	110	24	1	13,400	82
46	2/23/19	3/ 1/19	3/ 1/19	3/ 6/19	3/ 6/19	3/ 6/19	12:00 p.m.	500	102.4	118	42	1	.....	..
47	2/23/19	3/ 1/19	3/ 1/19	3/ 2 19	3/ 2 19	3/ 5/19	4:00 p.m.	700	102.8	100	26	4	9,800	80
48	2/23/19	3/ 1/19	3/ 1/19	2/26/19	3/ 9/19	3/12/19	12:30 p.m.	100	100.6	90	24	.....	12,400	84
49	2/23/19	3/ 1/19	3/ 1/19	3/ 2/19	3/ 7/19	3/ 8/19	5:00 a.m.	500	102.6	108	32	2	14,400	75
50	Camp organization			3/11/19	3/12/19	3/13/19	11:30 a.m.	400	105.4	114	22	2-3	9,600	80
51	Camp organization			3/11/19	3/ 5/19	3/14/19	4:00 p.m.	125	100	98	20	5	7,800	74
52	2/23/19	3/ 1/19	3/ 1/19	2/22/19	3/ 5/19	3/ 7/19	5:00 p.m.	300	99.4	104	22	5	33,200	85
53	2/23/19	3/ 1/19	3/ 1/19	3/ 8/19	3/10/19	3/12/19	12:15 a.m.	400	105	138	48	2	8,000	63
54	2/23/19	3/ 1/19	3/ 1/19	3/ 6/19	3/ 9/19	3/12/19	.....	...	101.4	124	22	5	.....	..
55	2/23/19	3/ 1/19	3/ 1/19	2/22/19	3/ 2/19	3/ 4/19	8:30 p.m.	600	103.2	102	22	1-2-3	13,200	85
56	2/16/19	2/24/19	2/24/19	2/26/19	2/27/19	2/27/19	8:30 p.m.	700	104.4	110	24	1-2-3	11,400	71
57	2/23/19	3/ 1/19	2/ 1/19	2/28/19	3/ 5/19	3/ 6/19	4:00 p.m.	900	104.4	124	24	4	28,600	91
58	2/23/19	3/ 1/19	3/ 1/19	2/22/19	2/26/19	2/27/19	4:00 p.m.	300	103	104	32	1	.....	..
59	Camp organization			3/ 7/19	3/ 8/19	3/ 9/19	10:00 a.m.	780	105	120	36	1	50,200	96
60	2/23/19	3/ 1/19	3/ 1/19	2/22/19	3/ 3/19	3/ 5/19	8:00 p.m.	600	102.2	128	28	4-5	.....	..
61	2/23/19	3/ 1/19	3/ 1/19	2/25/19	3/ 3/19	3/ 4/19	8:00 p.m.	400	103.8	110	38	3 5	.....	..
62	2/ 3/19	2/11/19	2/12/19	2/15/19	2/16/19	2/17/19	10:00 p.m.	200	100	84	20	4-5	19,600	87
63	2/16/19	2/24/19	2/24/19	2/25/19	3/ 2/19	3/ 3/19	.....	...	103.2	94	28	3	.....	..
64	Camp organization			3/ 6/19	3/ 7/19	3/ 7/19	12:00 p.m.	200	103	110	26	3	29,200	91
65	Camp organization			2/20/19	2/20/19	2/22/19	10:30 p.m.	300	103.6	120	24	4-5	24,000	89
66	2/23/19	3/ 1/19	3/ 1/19	3/ 1/19	3/ 2/19	3/ 4/19	8:00 p.m.	700	101.4	96	24	5	.....	..
67	2/23/19	3/ 1/19	3/ 1/19	2/28/19	3/ 3/19	3/ 5/19	4:00 p.m.	200	101.4	76	20	4-5	.....	..
68	2/23/19	3/ 1/19	3/ 1/19	3/ 1/19	3/ 4/19	3/ 7/19	.....	...	101.3	96	28	1-2-3 5	26,800	83

## —CASES OF TYPE I PNEUMONIA—(Continued)

Urine		Roentgen-Ray Findings Lobes 1-2-3-4-5 Number of Lobe	Blood Culture	Date of		Date of		Remarks: Complications and Necropsy Findings
Albumin	Casts			Crisis	Lysis	Duty	Death	
1 plus	2 plus	1-2	.....	2/30/19	.....	3/22/19	.....	Delirium
Neg.*	Neg.	1-2	.....	3/10/19	.....	3/25/19	.....	Leukocyte count after crisis
1 plus	1 plus	2-3 partial of 1	.....	3/11/19	.....	3/25/19	.....	Leukocyte count 1 week after crisis
1 plus	1 plus	1- 4-5	.....	3/ 5/19	.....	3/25/19	.....	
1 plus	1 plus	Broncho 4-5	.....	.....	3/8 to 3/12/19	4/ 5/19	.....	
1 plus	3 plus	.....	.....	3/ 9/19	.....	4/ 5/19	.....	Atypical crisis followed by irregular temp.
1 plus	Neg.	1	.....	3/ 9/19	.....	3/26/19	.....	
1 plus	Neg.	.....	.....	.....	3/8 to 3/10/19	3/26/18	.....	
1 plus	Neg.	4-5	.....	.....	3/6 to 3/10/19	4/ 1/19	.....	
Neg.	Neg.	2	.....	.....	3/10 to 3/14/19	3/29/19	.....	Admitted in convalescence
1 plus	2 plus	2-2	.....	3/ 9/19	.....	3/29/19	.....	
Neg.	Neg.	2-3	.....	.....	3/12 to 3/16/19	4/15/19	.....	Serum reaction marked
1 plus	1 plus	5	.....	.....	3/14 to 3/15/19	4/ 5/19	.....	Serum reaction marked
1 plus	1 plus	Lungs neg. for fluid	.....	3/ 8/19	.....	4/15/19	.....	
Neg.	Neg.	1	.....	3/13/19	.....	4/ 5/19	.....	Atypical crisis
Neg.	Neg.	.....	.....	3/10/19	.....	4/15/19	.....	No serum, temperature dropped from 105 to 98.6 in 16 hours
1 plus	3 plus	1-2-3 -5	.....	.....	3/6 to 3/9/19	4/29/19	.....	Serum reaction marked, delayed resolution
1 plus	2 plus	1-2-3 fluid at base	.....	.....	3/2 to ?	5/27/19	.....	Sterile fluid at right base, delayed resolution
1 plus	2 plus	5 and base of 4	Sterile	.....	3/9 to 3/11/19	4/ 5/19	.....	Meningismus, spinal fluid negative; serum reaction marked
1 plus	2 plus	.....	.....	2/28/19	.....	3/12/19	.....	
Neg.	Neg.	1-2	Sterile	Temp. 99.6 at death	.....	.....	3/23/19	Otitis media Type I, also K. L. found in throat and ear
3 plus	1 plus	.....	.....	Temp. 102.8 at death	.....	3/ 9/19	.....	Necropsy—Lobe 1 consol., fibrin. exudate; 2, 3, 4, 5 bronchopneumonia; mastoiditis rt. pn. Type I; meninges negative
Neg.	Neg.	.....	.....	Temp. 97.4 at death	.....	3/ 9/19	.....	Marked toxemia
1 plus	1 plus	.....	.....	3/18/19	.....	3/ 4/19	.....	Necropsy—Lobes 4 and 5 consol.; covered with fibrinous exudate
1 plus	3 plus	.....	.....	3/ 3/19	.....	3/18/19	.....	Marked toxemia
Neg.	Neg.	3	.....	3/ 8/19	.....	3/18/19	.....	Necropsy—Lobe 3 bluish red, solid throughout; 20 c.c. bloody fluid in pleural cavity; lobe 5 solid throughout
Neg.	Neg.	4-5 thickened pleura fluid base	.....	.....	2/21 to 2/23/19	5/12/19	.....	
1 plus	1 plus	4-5 fluid at base	.....	.....	3/6 to ?	5/13/19	.....	Empyema left, Type I
1 plus	1 plus	.....	.....	Temp. 100 at death	.....	.....	3/11/19	Abscess of left upper lobe with cavity
1 plus	1 plus	1-2-3	.....	Temp. 106.4 at death	.....	.....	3/17/19	Necropsy—Lobes 4 and 5 consol. and multiple abscesses throughout; pneumonia and tuberculosis present
								Entered hospital during convalescence
								Necropsy—Lobe 3 consol.; all lobes involved; much yellow exudate both chests

Of the sixty-one patients having the serum, thirty recovered by crisis, twenty-two by lysis and nine died. To the thirty who recovered by crisis a total amount of 8,665 c.c. was administered or an average dose of 288 c.c. Those ending in lysis received a total amount of 9,010 c.c., or an average dose per individual of 410 c.c. To those who died 3,200 c.c. were given, or an average dose per individual of 356 c.c.

In addition to the serum treatment, the general treatment was carried out. Each patient had 1,000 cu. ft. of air space. The windows were open day and night, and on sunny days the patients were moved to the porch. Rather large doses of digitalis and whisky were used during the critical stage, and codein was administered when a sedative was necessary.

The Rockefeller Institute states that the expected rate of mortality in this type of pneumonia where the serum is not used is 25 per cent. Their mortality rate with the use of the serum, in a series of 101 cases, was 7.5 per cent., using an average amount per individual of 250 c.c. Our mortality rate was 14.7 per cent. This higher death rate might be explained by a lower resistance to pneumonia in the colored race, the unfavorable season of the year and the forced moving of troops from place to place. Miller and Lusk in their report on pneumonia at Camp Dodge state that among sixty-nine cases of type I pneumonia, occurring in six months, in which no serum was used, the mortality rate was 2.8 per cent. We regret that we did not divide this series of cases into two groups, giving one half serum and the other half none.

We feel that this epidemic of type I pneumonia was caused by the close association of the men on the transports after being exposed to the inclement weather of Brest, as most of the cases developed on the boats or soon after landing.

We have used the type I serum in two cases of pneumonia with positive blood cultures, one with *Streptococcus viridans* and the other type IV pneumococcus. Each patient received eight injections after which the blood cultures of both were sterile and both recovered. This was done in desperation because of the death of three patients with positive blood cultures developing prior to these two.

## THE DETERMINATION OF HEMOGLOBIN BY THE ACID HEMATIN METHOD

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In the course of a study of the blood in the anemias of infancy, certain discrepancies were encountered in the acid hematin method of determination of hemoglobin described by Sahli.<sup>1</sup> The study of the cause of these discrepancies has led to a modification of the method to produce accurate determinations comparable with those obtainable when a determination of hemoglobin by measuring its iron content, or by the carbon monoxid hemoglobin method, is made. These modifications consist in: first, the use of N/10 hydrochloric acid as the diluent of the acid hematin instead of water; and second, the employment of heat to bring the reaction of formation of the acid hematin to its endpoint of equilibrium more quickly than it occurs in the cold.

Since the introduction of the acid hematin method by Sahli, various criticisms of it have been made. From the mechanical side these have been well summed up by Kuttner<sup>2</sup> as inaccuracies due to variations in the calibration and construction of the tubes, the fading of the standard and the variations in blood volume depending on the time when the blood is taken for examination. There are, in addition to these mechanical sources of error, certain chemical conditions of inaccuracy in the determination. These do not seem to have been considered at all in most of the literature concerned with the hemoglobin content of the blood in health and disease. These are: First, variation in the hydrogen ion concentration of the final fluid obtained; and second, the effect of time on the amount of acid hematin formed. Disregard of these factors, which are closely dependent, is why two observers will often disagree about a hemoglobin determination made upon the same individual by the Sahli method.

As regards the factor of variation in the hydrogen ion concentration, Sahli stipulated that acid should not be added beyond the 10 mark on the calibrated tube. As shown by Stäubli,<sup>3</sup> however, the addition of acid up to the 12 mark, alone, results in an appreciable variation in the reading. This can be seen in Table 1. Now, it is obvious that it is difficult in ordinary clinical work, and working with ordinary clinical instruments, not to pass a trifle beyond the 10 mark. Progress-

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1. Sahli: *Lehrbuch d. Klin. Untersuch. Methode*, 1909, Ed. 5, p. 846.

2. Kuttner: *J. A. M. A.* **66**:1370 (April 29) 1916.

3. Stäubli: *München. med. Wehnschr.* **58**:2429, 1911.

sive increase in the hydrogen ion content, by adding more and more acid produces corresponding variations. By using N/10 HCl throughout a determination, one can eliminate this source of error.

TABLE 1.—VARIATION OF HEMOGLOBIN READING WITH CONCENTRATION OF ACID AND TIME

Acid Mark	One Minute Reading, Per Cent.	Twenty Minute Reading, Per Cent.
10.....	70	70
13.....	70	80
15.....	75	90
18.....	80	95
20.....	85	100
22.....	90	110

When N/10 HCl is used throughout a determination, a progressive increase in the darkening of the fluid, that is a progressive increase in the amount of acid hematin formed, occurs. This does not occur with the method of Sahli when only normal values are under consideration. But as noticed by Stäubli, with lower values, that is, those which occur in clinical work, a distinct change in the darkening occurs from the first minute until the end of twenty to forty minutes, so that a final reading should not be made until it has been found that the color remains constant. Meyer and Butterfield<sup>4</sup> have also mentioned this variation in the color of acid hematin until equilibrium is established. Recently Newcomer<sup>5</sup> studied the absorption spectra of acid hematin and showed that the rate of formation of acid hematin is a rectangular hyperbola of the form  $xy = -c$ , and that an approximate equilibrium is not established until the lapse of from twenty to forty minutes. This is illustrated in Table 2.

TABLE 2.—VARIATION OF HEMOGLOBIN READING WITH TIME (HYDROGEN ION CONCENTRATION CONSTANT [10 MARK], DETERMINATION CARRIED OUT STRICTLY ACCORDING TO THE DIRECTIONS OF SAHLI)

One Minute, Per Cent.	Ten Minutes, Per Cent.	Twenty Minutes, Per Cent.	Forty Minutes, Per Cent.
60	75	80	80
50	70	85	85
45	60	65	65
55	70	70	70
60	75	80	80
45	60	65	65
70	75	75	75
65	75	80	80
30	50	55	60
40	60	70	70

To wait twenty minutes in clinical work is relatively a long time. As the time interval is apparently consumed in bringing the reaction

4. Meyer and Butterfield: Arch. Int. Med. **14**:94 (July) 1914.

5. Newcomer: J. Biol. Chem. **37**:465 (March) 1919.

of formation of the acid hematin to its end point, the effect of heat in hastening it was studied. It was found that boiling for one minute over a free flame, after a reading made at the end of one minute, using N/10 hydrochloric acid as a diluent throughout, and then making a reading at the end of another minute, gave a reading equal to the one obtainable after waiting for twenty minutes at room temperature. The deeper color obtained when N/10 HCl is used as a diluent makes a more accurate comparison possible according to a general principle of colorimetry.

Determinations of the absolute hemoglobin based on the iron content by the author's method<sup>6</sup> gave readings corresponding to those calculated on the basis of the final reading. This is shown in Table 3. Determinations of the hemoglobin by the carbon-monoxid hemoglobin method of Palmer<sup>7</sup> also showed close agreement. This is shown in Table 4.

TABLE 3.—HEMOGLOBIN DETERMINATIONS COMPARED WITH IRON CONTENT OF BLOOD

Reading At Room Tem- perature After Twenty Minutes, Per Cent.	Reading After Boiling for One Minute, Per Cent.	Hemoglobin Calculated from Iron Content, Per Cent.
95	95	93
90	90	90
105	105	106
80	80	78
95	95	96
100	100	100
70	70	72
60	60	58
90	90	91
55	55	57

TABLE 4.—HEMOGLOBIN DETERMINATION COMPARED WITH DETERMINATION BY PALMER METHOD

Acid Hematin Method, Per Cent.	Palmer Method, Per Cent.	Acid Hematin Method, Per Cent.	Palmer Method, Per Cent.
65.....	67	60.....	61
80.....	80	70.....	73
55.....	54	65.....	66
60.....	62	85.....	82
75.....	75	45.....	44

#### SUMMARY OF METHOD

To obtain a rapid, accurate determination of hemoglobin with clinical instruments, using the acid hematin method which requires the least amount of time, material and training, the following steps are gone through: The blood is obtained with a carefully calibrated pipette, preferably when the patient has not yet had the first meal of

6. Berman: J. Biol. Chem. **35**:231 (Aug.) 1918.

7. Palmer: J. Biol. Chem. **33**:119 (Jan.) 1918.

the day. It is diluted with N/10 HCl and a reading is made at the end of one minute. Then the fluid in the calibrated tube is carefully boiled over the free flame for one minute. After permitting to cool for one minute it is again diluted with N/10 HCl and a final reading made. A standard similarly constructed with a known normal blood should be used, and be made freshly daily, to avoid error due to fading.

#### CONCLUSIONS

1. The method of Sahli does not furnish accurate determinations of hemoglobin within from 15 to 20 per cent.
2. A method is described by which an accurate reading may be rapidly obtained with the ordinary clinical instrument.

I am indebted to Dr. Charles Gilmore Kerley of New York for much of the material on which this study has been based, and also to Dr. Donald Van Slyke of the Rockefeller Institute for helpful assistance.

# A STUDY OF THE RENAL CONCENTRATION POWER FOR URIC ACID IN EARLY CHRONIC INTERSTITIAL NEPHRITIS

PRELIMINARY PAPER

ROY UPHAM, M.D., AND HENRY ALLEN HIGLEY, M.D.

BROOKLYN

In 1916 Myers and Fine<sup>1</sup> published a series of cases showing an increase of blood uric acid in early chronic interstitial nephritis. In later cases of this disease they showed an increase of blood urea and creatinin. Subsequently, in 1919 the same authors<sup>2</sup> drew attention to the fact that uric acid, urea and creatinin pass through the renal membrane with different degrees of ease. The kidney concentrates uric acid approximately twenty times, while it concentrates urea and creatinin approximately eighty and one hundred times, respectively.

With the above work as a point of departure, we instituted a series of studies regarding the renal concentration power for uric acid in early chronic interstitial nephritis with the thought that the findings might be utilized for accurate results in the early diagnosis of that disease.

The scope of the work is naturally divided as follows:

1. A study of the renal concentration power for uric acid in early chronic interstitial nephritis.
2. A study of the renal concentration power for uric acid in the nonnephritic kidney.
3. A study of the renal concentration power for uric acid in cases showing indefinite clinical or urinary symptoms, in which a diagnosis of nephritis is not possible by present methods—the subsequent development of such cases to be observed carefully.

With this classification in view, we have studied a number of successive cases as they presented themselves to one of us and a preliminary report of the work is here presented.

## STANDARDIZATION OF OBSERVATION

In estimating the blood content of uric acid, the prevalent practice is to obtain the blood specimen before breakfast, the patient having been for a certain period on a diet low in nucleo-proteids. Such procedure is obligatory in order to eliminate the variable blood content of uric acid due to diet. Only by such regulation has it been possible to obtain a certain uniformity of standard.

1. Myers and Fine: Arch. Int. Med. **17**:570 (April) 1916.

2. Myers and Fine: J. Biol. Chem. **32**:239 (Feb.) 1919.

In the present work such restrictions, however, have been considered by us undesirable for the following reasons:

1. In our study the actual blood and urine contents of uric acid are not important, the renal concentration power, which is sought, being obtained merely by the relation of the urine uric acid to the blood uric acid.

2. Under restricted diet the body metabolism is reduced and the functioning power of the body organs lessened. In estimating the renal concentration power it is not desirable that the functioning of the kidneys be reduced by purely dietary factors.

3. In the series of cases referred to in the initial paragraph of this article, Myers and Fine show that in early nephritis the blood uric acid content is but little elevated so that the concentration power of the kidney, in such cases, approaches the normal. In studying such cases, therefore, the diet should be such that the concentration power of the kidney can be observed under conditions of more or less stress.

Since the fluid intake, in all probability, influences the renal concentration power, at least so far as separate voidings of urine are concerned, for uniformity of observation, such was standardized as approximately normal.

The patients under observation were, therefore, placed on the following diet and fluid intake for forty-eight hours previous to taking the blood and urine specimens. These were taken simultaneously between 11 and 12 a. m.

#### DIET

Eat exactly according to this diet, both as to the quantity and particular articles of diet.

#### ON ARISING:

Drink 16 ounces of water.....

#### BREAKFAST:

Calories

4 tablespoonfuls of cream of wheat, hominy or oatmeal.....	100
3 ounces of cream.....	150
1 slice bread.....	100
1 pat of butter, 1 by 1 by $\frac{1}{4}$ inches.....	100
1 soft egg.....	100
8 ounces of cocoa.....	240
8 ounces of water.....	

Total calories for breakfast..... 790

#### NOON:

8 ounces of puree of pea, bean or potato.....	200
2 lamb chops.....	200
1 baked potato.....	100
1 pat of butter.....	100
4 tablespoonfuls of junket.....	80
1 slice of bread.....	100
1 pat of butter.....	100
8 ounces of water.....	

Total calories for noon meal..... 880

6 P. M.:

1 slice bread.....	100
1 slice roast beef.....	100
6 tablespoonfuls of green vegetables, string beans, cauliflower, cabbage, etc. ....	100
1 pat of butter.....	100
8 ounces of water.....	
6 tablespoonfuls of rice pudding, corn starch or custard.....	300
3 ounces of cream.....	150
6 ounces of milk.....	120

Total calories for evening meal..... 970

10 P. M.:

8 ounces of cocoa.....	240	240
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Total calories for all meals..... 2,880

On the day the test is made, void urine prior to meals only and retain urine after meals until the time test is taken.

## TECHNIC

*Quantitative Method for Blood Uric Acid.*—The colorimeter used was that of Benedict and Bock.

The method employed was that of Folin and Denis as modified by Benedict and Hitchcock. The amount of blood used for each test was 10 c.c. The specimen was not oxalated, but was at once mixed with 50 c.c. of hundredth normal acetic acid and immediately placed on the water bath. Special care was taken to obtain a good coagulum over the water bath before the mixture was boiled over the free flame. In every instance the total filtrate for evaporation was kept between 125 and 150 c.c. After the addition of the silver-ammonia-magnesia mixture to the concentrated filtrate, care was taken to keep the specimen long enough in the icebox to obtain complete separation before centrifuging. In no instance was the icebox time less than thirty minutes. In case of doubt in accurately matching the colors, that reading was taken which when computed would give the lowest amount of uric acid. Since it is well known that by the above method about 90 per cent. of the blood uric acid is extracted, 10 per cent. of the amount computed was added to give the final figures for blood uric acid.

*Quantitative Method for Urine Uric Acid.*—The method employed was that of Benedict and Hitchcock. The same precautions were taken for obtaining complete separation in the icebox as mentioned under blood uric acid. In cases of doubt in accurately matching the colors, that reading was taken which when computed would give the lowest amount of uric acid.

The renal concentration power was computed by dividing the amount of urine uric acid by the amount of blood uric acid, and it

should be noted that from the preceding in every instance the highest concentration power possible for that case was thus recorded.

#### DISCUSSION

We have accepted 3 mg. per 100 c.c. as the high normal limit for blood uric acid.

It is interesting to note that so far as blood uric acid content in early chronic interstitial nephritis is concerned, our figures as shown by Group 1 are in accord with the findings of Myers and Fine, mentioned at the beginning of this article and also with the more recent work of Baumann, Hausmann, Davis and Stevens.<sup>3</sup> High figures for blood uric acid were obtained in 85.6 per cent. of our cases of nephritis. On the other hand, 40 per cent. of our cases of negative nephritis also gave high figures for blood uric acid. This would indicate that while high blood uric acid is an exceedingly common symptom of early chronic interstitial nephritis, it is by no means a specific one. Its availability for the early accurate diagnosis of that disease is, therefore, materially limited.

It is also important to notice that in early chronic interstitial nephritis the height of blood uric acid increase is not a guide to the degree of impairment of the renal concentration power. There is no direct relation between the amounts of blood uric acid and the concentration of figures. Thus in Group 1, Cases 7 and 13, which are among the highest in blood uric acid, show the better concentration figures, while Cases 8 and 11, which show the lowest and practically normal amounts for blood uric acid, give much worse concentration figures. On the other hand, Cases 4 and 14, which are high in blood uric acid, give exceedingly poor concentration figures, and Cases 1 and 12, in which blood uric acid is only slightly elevated, show very fair concentration figures. In early chronic interstitial nephritis, therefore, the degree of impairment of the renal concentration function is not accurately gaged by mere blood uric acid content.

It is of special importance to note that the nonnephritic kidney shows a condition which is the direct opposite of the foregoing. In the nonnephritic kidney there is a direct relation between the blood uric acid content and the concentration figure. From Group 2, with the exception of Case 5, it is seen that the higher the blood uric acid content, the lower the concentration figure, and the lower the blood uric acid, the higher the concentration figure. In the nonnephritic, therefore, it would seem that as the blood uric acid content rises, the renal concentration power falls, and as the blood uric acid content

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3. Baumann, Hausmann, Davis and Stevens: *Arch. Int. Med.* **24**:70 (July) 1919.

TABLE 1.—GROUP 1. CASES OF POSITIVE CHRONIC INTERSTITIAL NEPHRITIS

No. Name	Age	Blood Pressure	Cardiac Area Verified by Roentgenograms	Cardiac Murmur	Brachials	Headache	Vertigo	Vision	Eye Ground	Loss of Weight	Digestive Disturbances	Albumin	Casts	Blood Uric Acid, Mg. per 100 C.c.	Urine Uric Acid, Mg. per 100 C.c.	Renal Concentration
1. A. W. A.	49	170	Increased	—	—	+	+	+	+	+	+	+	—	3.16	38.8	12.2
2. G. W. B.	52	140	—	—	—	+	+	+	+	+	+	+	—	3.87	17.0	4.4
3. J. B.	45	122	—	—	—	+	+	+	+	+	+	+	—	5.11	19.48	3.8
4. A. W. B.	60	170	Increased	—	—	+	+	+	+	+	+	+	—	6.27	22.0	3.5
5. C. C. B.	46	112	—	—	—	+	+	+	+	+	+	+	—	4.12	24.0	5.8
6. J. F. H.	57	170	Increased	—	—	+	+	+	+	+	+	+	—	4.96	37.5	7.5
7. M. H.	70	165	Increased	—	—	+	+	+	+	+	+	+	—	6.24	64.0	10.2
8. R. J.	50	190	Increased	—	—	+	+	+	+	+	+	+	—	2.24	15.6	7.0
9. J. M.	62	160	Increased	—	—	+	+	+	+	+	+	+	—	2.48	21.84	6.0
10. M. V. A.	58	154	—	—	—	+	+	+	+	+	+	+	—	5.72	15.0	2.6
11. M. B.	58	198	Increased	—	—	+	+	+	+	+	+	+	—	3.02	13.12	4.3
12. H. H.	14	110	—	—	—	+	+	+	+	+	+	+	—	4.00	56.0	14.0
13. W. H. D.	65	190	Increased	—	—	+	+	+	+	+	+	+	—	9.25	107.0	12.9
14. O. F.	46	110	Increased	—	—	+	+	+	+	+	+	+	—	7.42	32.88	4.4

TABLE 2.—GROUP 2. CASES OF NEGATIVE NEPHRITIS

No. Name	Age	Blood Pressure	Cardiac Area Verified by Roentgenograms	Cardiac Murmur	Brachials	Headache	Vertigo	Vision	Eye Ground	Loss of Weight	Digestive Disturbances	Albumin	Casts	Blood Uric Acid, Mg. per 100 C.c.	Urine Uric Acid, Mg. per 100 C.c.	Renal Concentration
1. R. R. B.	31	120	—	—	—	—	—	—	—	—	—	—	—	2.06	53.7	26.1
2. F. H.	38	108	—	—	—	—	—	—	—	—	—	—	—	4.58	93.5	20.4
3. R. A. S.	40	120	—	—	—	—	—	—	—	—	—	—	—	1.50	54.0	36.0
4. C. N. J.	46	114	Increased	+	+	+	—	—	—	—	—	—	—	2.44	50.0	20.5
5. H. A. H.	53	140	—	—	—	—	—	—	—	—	—	—	—	2.42	59.5	24.6
6. H. W. H.	52	143	—	—	—	—	—	—	—	—	—	—	—	5.20	104.0	20.0
7. C. H.	25	125	—	—	—	—	—	—	—	—	—	—	—	4.63	103.7	22.4
8. W. H.	20	120	—	—	—	—	—	—	—	—	—	—	—	1.85	59.9	32.4
9. F. D.	30	130	—	—	—	—	—	—	—	—	—	—	—	2.60	65.2	25.1
10. A. D.	35	135	—	—	—	—	—	—	—	—	—	—	—	4.75	101.1	21.3

TABLE 3.—GROUP 3. QUESTIONABLE CASES OF CHRONIC INTERSTITIAL NEPHRITIS

No. Name	Age	Blood Pressure	Cardiac Area Verified by Roentgenograms	Cardiac Murmur	Brachials	Headache	Vertigo	Vision	Eye Ground	Loss of Weight	Digestive Disturbances	Albumin	Casts	Blood Uric Acid, Mg. per 100 C.c.	Urine Uric Acid, Mg. per 100 C.c.	Renal Concentration
1. F. S. D.	32	90	—	—	—	—	—	—	—	—	—	—	—	1.76	12.5	7.1
2. M. H.	33	118	—	—	—	—	—	—	—	—	—	—	—	2.66	18.0	6.7
3. A. J.	23	140	—	—	—	—	—	—	—	—	—	—	—	4.00	51.0	12.7
4. R. R. R.	59	140	+	+	+	+	+	+	+	+	+	+	—	3.61	66.5	18.4
5. M. S.	33	130	—	—	—	—	—	—	—	—	—	—	—	4.02	44.4	11.0
6. R. W.	38	140	+	+	+	+	+	+	+	+	+	+	—	3.36	38.0	11.0
7. E. H. W.	39	122	+	+	+	+	+	+	+	+	+	+	—	4.1	66.0	16.1
8. H. D. S.	55	175	+	+	+	+	+	+	+	+	+	+	—	2.64	37.5	14.2
9. A. R.	43	125	—	—	—	—	—	—	—	—	—	—	—	3.92	47.1	12.0
10. L. M.	49	155	—	—	—	—	—	—	—	—	—	—	—	6.96	107.0	15.3

falls the renal concentration power rises. We are now engaged in a series of studies in order to ascertain to what extent this characteristic may be utilized in differentiating the nonnephritic from the nephritic kidney.

The perspective of the concentration figures is best obtained by a consideration of the cases in their clinical groups, as follows:

1. A group (No. 1) which shows clinical symptoms diagnostic of nephritis. These all show a concentration figure of 14 or below.

2. A group (No. 2) which shows no clinical symptoms suggestive or diagnostic of nephritis. These all show a concentration figure of 20 or above.

The divergence in concentration figures between these two groups (nephritics and nonnephritics) is definite and marked. Such figures give a clean-cut division which leaves no room for doubt. No such clean-cut division is afforded by the figures for the blood uric acid contents.

3. A group (No. 3) which shows clinical symptoms suggestive but not diagnostic of nephritis. These all show concentration figures below 18.4.

It is our belief that this group in reality belongs with the positive nephritics in Group 1, and that such belief will be verified by the further clinical observations of these cases. Such observations are now under way, together with the study of other cases both from a clinical and concentration standpoint.

A further study of the effects of treatment on the concentration figures of positive nephritics is being undertaken by us.

## ROENTGENOGRAPHIC STUDIES IN GOUT \*

C. W. McCLURE, M.D., AND E. D. McCARTY, M.D.

BOSTON

Certain bony changes are found in the roentgenogram which roentgenologists maintain are pathognomonic evidence of gout. Occasionally roentgenologists of this hospital have made the diagnosis of gout from the roentgen-ray findings in cases in which there were no clinical evidences of that disease. This led to the present investigation, the purpose of which was to establish the diagnostic value of such roentgenographic findings. The latter were first described as occurring in the roentgenogram of the phalanges in a case of gout by Huber<sup>1</sup> in 1896. His observations have been confirmed by several other writers. A report by Koehler<sup>2</sup> contains some excellent plates and diagrams of the roentgenographic findings considered as peculiar to gout. Drinberg<sup>3</sup> in a further contribution to the subject has collected the literature up to 1911. The best articles are those of Strangeways<sup>4</sup> and Jacobsohn.<sup>5</sup> All writers have agreed that the roentgenographic changes in the bones described by Huber are always the result of tophi, except Strangeways, who expresses no definite opinion. The changes have been found in the bones of wrists, hands, ankles and feet.

We have investigated (1) the roentgenographic findings in the bones of the wrists, hands, ankles and feet of gouty patients, and (2) the frequency of the so-called pathognomonic gouty bony changes in the same anatomic regions in cases of chronic arthritis which were clinically not gout. A detailed report of the roentgenographic findings in nine gouty cases is made. All these patients had tophi from which sodium urate crystals were obtained. One case which was clinically not gout is described for purposes of comparison. This case had been diagnosed gout by a former roentgenologist of the hospital.

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\*From the Medical Clinic and the Roentgenographic Department of the Peter Bent Brigham Hospital.

1. Huber: Ein Fall von Gichtthand unter Roentgenbilde, Deutsch. med. Wchnschr. **22**:182, 1896.

2. Koehler, A.: Typical Alterations of the Bones in Gout, Arch. Roentg. Ray **16**:330 1911.

3. Drinberg, E.: Die Gicht in Röntgenbilde, Diss., Berlin, 1911.

4. Strangeways, T. S. P.: A Study of Joints from Cases of Rheumatoid Arthritis and Chronic Gout by Means of Skiagrams, and Dissection of the Affected Parts, Bull. of the Committee for the Study of Special Diseases **1**: 2: 87, 1905-1910. A Study of Skiagrams from the Hands of One Hundred Cases of So-Called Rheumatoid Arthritis and Chronic Gout, Ibid., 145.

5. Jacobsohn, E.: Die Arthritis Urica im Röntgenbilde, Mitt. a. d. Grenzgeb. d. Med. u. Chirug. **26**:531, 1913.

The so-called gouty changes in the roentgenograms of the bones are represented by discrete, circular or oval areas of decreased density; that is, areas of rarefaction (Figs. 1, 2, 3, 4). These areas form segments of a circle when they occur in the edges of the bones. The borders of the areas are more or less distinct and often are very sharply defined. In the following roentgen reports the areas are designated as "focal areas of decreased density." The phrase "proliferative changes" is used to describe lipping and spur formation at the margins of the articular surfaces of bones. "Atrophy" designates the appearance in the roentgenogram resulting from partial absorption of the lime salts from bones. "Destruction" is used to designate irregular areas in which it appears as though complete absorption of bone had occurred.

#### REPORT OF CASES

CASE 1 (Med. No. 5278).—W. H. K.; woman; white; aged 29 years.

Diagnosis: Chronic arthritis.

The patient's habits were good. She had had chronic polyarthritis with occasional fairly acute exacerbations for the previous two years. The joints never had been severely painful or tender. During the previous six months stiffness of the knees had prevented walking. Physical examination was negative, except for the joints. There was limitation of motion and crepitation in all joints of the extremities. The elbows, wrists, finger joints, knees and joints of both great toes were enlarged, principally as the result of thickening of the periarticular tissues. There were no tophi. Blood pressure was 110 mm. systolic and 75 mm. diastolic. Urine examinations were negative, except for a scant trace of albumin and a rare cast in one of the specimens. Phenolsulphonephthalein excretion was 65 per cent. in two hours. Uric acid was 1.5 mg. and nonprotein nitrogen 28 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 7912).—Hands and wrists: The lower ends of the radii, ulnae, all the bones of both carpi, of both metacarpi and of all the phalanges show marked atrophy (Fig. 1). The radio-ulnar-carpal joint space of each wrist is narrowed. The articular surfaces of both radii and ulnae are irregular in outline and show slight proliferative changes. The joint spaces in both carpi are narrowed. The heads of the left second and of the right third metacarpal bones are irregularly semicircular in outline due to partial bony destruction. In the right hand the first, second, third and fifth and in the left hand the first and second metacarpophalangeal joint spaces are narrowed. With the exception of the terminal joints of each little finger all the interphalangeal joints are narrowed or obliterated. The first interphalangeal joints of the second, third and fifth fingers of the left hand, of the third and fifth fingers of the right hand, and the second interphalangeal joint of the third finger of this hand are obliterated and replaced by mottled areas of increased density. About these joints and about the bases of the proximal phalanges of both index fingers there are proliferative changes. The distal articular surfaces of the radii and ulnae present several more or less circular areas of decreased density from 1 to 3 mm. in diameter. In the right hand are irregular areas of decreased density. These areas are several millimeters in diameter. There is fusiform thickening of the soft tissues overlying those phalangeal joints which are obliterated.

Knees: All bones of the knee joints show bony atrophy, more marked in the left knee. The condyles of the femurs and the under surface of the left patella are irregular in outline. The under surface of the right patella shows slight lipping.

**Feet:** All the bones of the feet show atrophy (Fig. 2). This is most marked in the tarsi and metatarsi. The plantar arches are high. The articular ends of the heads of the first, second, third and fifth metatarsal bones of the right foot and the first and second of the left show varying degrees of destruction, some of them being almost completely destroyed. The outlines of the remaining portions of the articular ends of these bones present a scalloped appearance due to notching with more or less semicircular areas of complete destruction. There is irregularity in the outline of the articular surfaces of the bases of the outer four phalanges of both feet. There is a small area



Fig. 1.—Roentgenogram of the hands in Case 1.

of bony density lying just to the mesial side of the head of the fifth metatarsal bone of the right foot. The metacarpophalangeal joint space of each hallux is narrowed and the articular surfaces are decreased in density and irregular in outline. In the head of each first metatarsal bone is a focal area of decreased density. These two areas are nearly circular in outline, their diameters are about 4 mm. and their borders are not sharply defined.

## SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Atrophic changes involve all the bones of the hands, wrists, feet and knees. Destructive changes involve many of the bones of the hands. The terminal interphalangeal joints of both little fingers are normal. The third and fourth metacarpophalangeal joint spaces of the left hand are very slightly narrowed. All other joint spaces of the hands, wrists and feet are narrowed, obliterated or else distorted by position. There are slight proliferative changes about some of the joints. Focal areas of decreased density are found.

CASE 2 (Med. No. 5421).—J. G.; white, male, aged 57 years.

Diagnosis: Gout; arteriosclerosis; hypertension; chronic myocarditis; very questionable chronic nephritis.

The patient had used beer freely. He had had about sixteen attacks of severe polyarthritis of gouty character during the previous twenty-six years. Physical examination showed numerous tophi in the ears and on the fingers. The joints showed the changes of chronic arthritis. The radial artery walls were sclerosed. The blood pressure was 185 mm. systolic and 117 mm. diastolic. Otherwise physical examination was negative. The urine examinations were negative. Phenolsulphonephthalein excretion was 52 per cent. in two hours. The uric acid was 5 mg. and the nonprotein nitrogen 38 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 8140).—Hands and wrists: There is moderate bony atrophy of the lower ends of the radii, ulnae, all the bones of the carpi, metacarpal and phalanges (Fig. 3). Proliferative changes involve most of the articular ends of the phalanges and of the distal ends of the metacarpals. The bones of the wrists show mottling, due to small areas of decreased and increased density. All the joint spaces of the wrists are narrowed and there is some irregularity in outline of the articular surfaces of the bones. The heads of the metacarpal bones, except the fourth metacarpals, of both hands show spur formation and more or less mottling. The metacarpophalangeal articular surfaces of the bones are irregular in outline, the articular margins show variable degrees of increased density and the corresponding joint spaces are narrowed. These changes are most pronounced in the metacarpophalangeal joint of the right middle finger, the articular surfaces being completely destroyed and replaced by an irregular density. The metacarpophalangeal joint of the right ring finger is normal except for slight narrowing of the joint space. The interphalangeal joints present various degrees of the same processes described in the metacarpophalangeal joints. Some of the interphalangeal joints are normal in appearance. Others, especially the proximal interphalangeal joints of the fourth and fifth phalanges of the left hand, are more or less obliterated and replaced by deposits of increased density with proliferative changes (lipping and spur formation). The shaft of the middle phalanx of the middle finger of the right hand is narrowed. There are numerous more or less circular, frequently fairly well defined focal areas of decreased density, localized mostly in the heads of the metacarpal and phalangeal bones.

The soft tissues of the fingers show irregular nodular thickenings. The larger arteries of the forearms and wrists are visible.

Knees: Proliferative changes involve the articulating surfaces of all the bones of both knee joints. There is lipping of the tuberosities of both femurs. The popliteal arteries and their larger branches are plainly visible.

Feet: The plantar arches are high. There is a moderate amount of bony atrophy of all the bones of the feet. The tarsal bones present a mottled appearance due to small areas of alternating increased and decreased density. The tarsal joint spaces are narrowed; some of them are obliterated and replaced by irregular lines of increased density. All these changes are more pronounced in the left foot. The heads of both first metatarsal bones are mottled. The margins of their phalangeal articular surfaces show lipping and the corre-

sponding joint spaces are narrowed. The head of the second metatarsal bone of the right foot shows proliferative changes. The heads of both fifth metatarsal bones are irregular in outline. The articulating surfaces of the bones forming the metatarsophalangeal joints of both fifth metatarsals are irregular in outline. There is partial subluxation of the bones of the fifth metatarsophalangeal joint of the right foot. The rest of the metatarsophalangeal joint spaces show varying degrees of narrowing. The interphalangeal joint spaces of the halluces are narrowed and there is lipping at the margins of the articular surfaces. Both great toes show a moderate degree of hallux valgus.

In the heads of both first, both fifth and the right second metatarsal bones are focal areas of decreased density. The latter tend to be circular in outline, the borders are more or less well defined and vary in diameter from 1 to 5 mm. The soft tissues in the regions of the first and fifth metatarsophalangeal



Fig. 2.—Roentgenogram of the metatarsals and phalanges of the feet in Case 1.

articulation of both feet show slight nodular thickening. The larger arteries of the feet are visible.

#### SUMMARY OF ROENTGENOGRAPHIC FINDINGS

The changes found are atrophic, proliferative and destructive in type. Certain bones and their joint surfaces are involved in these changes while others are normal or nearly normal. Some of the joint spaces are obliterated and ankylosis has occurred in certain of them. There is partial subluxation of one joint. There are focal areas of decreased density in some of the bones. The regions in which these areas occur usually show other bony changes. Nodular thickening of the soft tissues and arteriosclerosis of the larger vessels are present.

CASE 3 (Med. No. 5471).—W. P. G.; negro; male, aged 43 years.

Diagnosis: Gout; questionable chronic nephritis.

The patient's habits were good. During the last ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers. On physical examination numerous tophi were found in the ears and about the finger joints. Otherwise physical examination was negative. The blood pressure was 135 mm. systolic and 95 mm. diastolic. The urine contained no casts, no blood and no epithelium. A scant trace of albumin was found once in the examination of several urine specimens. Phenolsulphonephthalein excretion was 42 per cent. in two hours. The uric acid was 4 mg. and the nonprotein nitrogen 44 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 8225).—Hands and wrists: The radio-ulnar-carpal joint space of the left wrist is narrowed (Fig. 4). There is complete destruction of the distal end of the second phalanx and the proximal extremity of the terminal phalanx of the right little finger. The bony proximal and distal borders of the area of destruction form a curved line. The articular extremity of the terminal phalanx of the little finger of the left hand shows spur formation. The corresponding joint space is narrowed but the articular surfaces are smooth. The first phalanx of this finger shows a moderate degree of bony atrophy. In the index finger of the left hand the terminal joint space is obliterated. The first interphalangeal joint of this finger shows slight narrowing and there is slight lipping of the articular surfaces of the phalangeal bones. The major portion of the shaft of the second phalanx of this finger shows thickening at the expense of the medullary canal. The terminal phalanx shows proliferative changes. The terminal joint of the left thumb shows proliferative changes of the ends of the phalanges entering into its formation and there is slight narrowing of the joint space. The two phalanges of the left thumb show a moderate degree of bony atrophy. The remaining bones and joints of both hands and wrists are normal in appearance.

In the middle phalanx of the little finger of the left hand is a regular, circular area of decreased density 4 mm. in diameter. The bone immediately proximal to this area is increased in density, and just distal to it is decreased in density. In the proliferative changes of the terminal joint of the left index finger is an almost circular area of decreased density about 4 mm. in diameter. Similar areas lie proximal to it in the second phalanx and distal to it in the terminal phalanx of that finger. There is a well defined, circumscribed area of decreased density in the distal end of the first phalanx of the left thumb. In the proliferative changes on the palmar surface of this thumb, is a clearly defined circular area of decreased density 3 mm. in diameter. At the base of the styloid process of the left ulna is a small, rather irregular, well defined area of decreased density. The soft tissues of the fingers show many nodular areas of thickening.

Feet: The first metatarsophalangeal joint of the right foot is narrowed, the margins of the articular surfaces are increased in density, and show proliferative changes. The inner margins of the head of the first metacarpal bone and the adjacent phalanx of the left great toe show slight irregularity in outline. The articular ends of the phalanges entering into the terminal joint of this toe show proliferative changes. The remaining bones of the feet show no proliferative changes.

The internal portions of the heads of both first metatarsal bones show moderately well defined, circular areas of decreased density from 2 to 4 mm. in diameter. Two similar areas are present in the proximal end of the first phalanx of the right hallux. One of these areas is 3 mm. in diameter and involves the joint surface. The other area is 2 mm. in diameter and is situated in the external portion of the bone near the proximal joint. Two small circular areas of decreased density are present in the internal cuneiform bone of the right tarsus. There are no changes in the soft tissues.

## SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Proliferative, atrophic and destructive changes are found. Not all the bones and joint spaces are affected. In the feet all the bones show slight atrophy but the proliferative and destructive changes are irregularly distributed. Many focal areas of decreased density are present. Most of these are in areas showing other bony changes. The soft tissues of the fingers show nodular thickenings.

CASE 4 (Med. No. 5297).—A. L. E.; white, male, aged 48 years.

Diagnosis: Gout; cirrhosis of the liver; questionable nephritis.

The patient had used large quantities of beer and whisky for many years. In the previous five years the patient had had five attacks resembling more the exacerbations of chronic arthritis than gout. Three of these attacks occurred in the Peter Bent Brigham Hospital. Physical examination showed several tophi in the ears. The joints of the hands showed some periarticular thickening. The radial arteries were palpable. Blood pressure was 156 mm.



Fig. 3.—Roentgenogram of the hands in Case 2.

systolic and 96 mm. diastolic. The liver edge was palpable 4 cm. below the right costal margin. Otherwise the physical examination was negative. The urine showed occasionally a scant trace of albumin and a few casts. Phenol-sulphonephthalein excretion was 24 per cent. in two hours. The uric acid was 5 mg. and the nonprotein nitrogen 53 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 1486).—Hands and wrists: The styloid processes of both ulnae are slightly irregular in outline. The joint spaces of both carpi are narrowed. The outlines of the carpal bones of both wrists are indistinct. The articular surfaces of the carpal bones of the right wrist show increased density. There is atrophy of the first metacarpal bone of the right hand. The

last two phalanges of the left little finger are atrophied, the interphalangeal joint is obliterated and shows proliferative changes. The terminal phalangeal joint of the ring finger of the right hand shows narrowing of the joint space and the articulating surfaces of the bones show lipping at their margins. The rest of the bones of the hand present no abnormalities.

In the right cuneiform bone is a well defined circular area of decreased density 1 mm. in diameter. Indenting the surface of the left metacarpal bone, just proximal to its head, is a small scalloped area of decreased density. Each styloid process contains a well defined, circular area of decreased density surrounded by normal appearing bone. In the outer margin of the proliferative changes in the left little finger is a well defined, circular area of decreased density 2 mm. in diameter. A similar area is present in the terminal phalanx of the ring finger of the right hand. The soft tissues show no changes.

#### SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Localized proliferative and slight atrophic bony changes are found. The majority of the bones and joints of the hands and feet appear normal. Focal areas of decreased bony density occur.

CASE 5 (Med. No. 2929).—G. W. L., white, male, aged 68 years.

Diagnosis: Gout.

The patient had been a very moderate user of alcoholic beverages. For the past twelve years the patient had had monoarticular and polyarticular attacks of arthritis characterized by great swelling, deep redness, exquisite tenderness and extreme pain in the affected joints. On physical examination tophi were found in the auricles of the ears. From them sodium urate crystals were obtained. Large tophi were numerous in the fingers and about the elbow joints and on the posterior aspect of the right heel. Otherwise the physical examination was essentially negative. The urine showed the very slightest traces of albumin and a variable number of hyaline casts. Phenolsulphone-phthalein excretion was 57 per cent. in two hours. Blood urea nitrogen was 19 mg. and uric acid 5 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 210).—Feet: The bones of both feet show slight atrophy which is more marked in the left foot. There is narrowing of both the first metatarsophalangeal joint spaces. There are proliferative changes involving the margins of the articular surfaces of the bases of the phalanges and the heads of the metatarsal bones of these joints. The heads of the first metatarsal bones are wider than normal. There is partial subluxation of the phalanx entering into the formation of the right fifth metatarsophalangeal joint. The inner portions of the heads of the first metatarsal bones of both feet are decreased in density and present a mottled appearance. The latter appearance is due to numerous focal areas of greater decreased density. All the phalanges except half of the first are missing from the toe of the left foot. There is hallux valgus of both sides. The mesial outline of the head of each first metatarsal bone is indented with a semicircular area, about 4 mm. in diameter, of complete bony absence. The semicircular areas are situated in proliferative bony changes. The outer surfaces of the heads of both fifth metatarsal bones are irregular in outline and show circular, fairly well defined focal areas of decreased density. There is slight thickening of the soft tissues over the metatarsophalangeal joint of the left hallux and also over the second phalanx of the left little toe.

#### SUMMARY OF ROENTGENOGRAPHIC FINDINGS

There is generalized bony atrophy. Proliferative changes are localized to the first metatarsophalangeal joints. The majority of the joints appear normal. Well defined focal areas of decreased density occur. There is hallux valgus.

CASE 6 (O. D. D. No. 36014).—J. F. S., white, male, aged 42 years.

Diagnosis: Gout.

The patient was a heavy beer drinker. He had had numerous attacks of monoarticular and of polyarticular arthritis of typical gouty character in the previous ten years. Physical examination was negative except for tophi in the ears, about the knuckle joints of the left hand and just above the olecranon processes of both ulnae. There were no evidences of cardiovascular disease. Blood pressure was 144 mm. systolic and 90 mm. diastolic. The urine contains no albumin but an occasional hyaline cast was found. Phenolsulphone-phthalein excretion was 38 per cent. in two hours. The nonprotein nitrogen was 48 mg. and uric acid 6 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 9216).—Hands and wrists: There is a moderate degree of atrophy of the lower end of the radius, ulna, the bones of the carpus,



Fig. 4.—Roentgenogram of the hands in Case 3.

metacarpals and phalanges of the left hand. There is a very slight amount of atrophy of the bones of the right carpus and hand. The carpal joints appear normal. The inner margin of the base of the first phalanx of the right hand shows proliferative changes. The articular surfaces of the bones forming the right third metacarpophalangeal joint are in contact and their outlines are irregular. There are proliferative changes of the ends of both the bones of this joint. The middle finger of the right hand is a little shorter than the corresponding finger of the left hand. The other joints of the hands appear normal. In the head of the first metacarpal bone of the right hand is a small, oval area of decreased density. A similar area is present in the proliferative changes described in the base of the first phalanx of the right index finger. On the dorsum of the right hand is a nodular area of thickening of the soft tissues about 5 cm. in diameter.

**Feet:** All the bones of the tarsi, metatarsi and phalanges show a moderate amount of atrophy. All the tarsal bones show slight mottling. The bases of the third, fourth and fifth metatarsal bones of the right foot show mottling. The tarsal and tarsometatarsal joints are for the most part not clearly defined in the plate, probably due to position. Those which are outlined appear normal. The terminal joint spaces on each foot are distorted by position. The remaining joint spaces of the feet are normal in appearance. There are slight proliferative changes at the margins of the articular surfaces of the bones entering into the formation of the first metatarsophalangeal joint of both feet. The inner portion of the head of each first metatarsal bone shows proliferative changes and is decreased in density and irregular in outline. The left great toe shows slight hallux valgus. The mesial outline of each first cuneiform bone is scalloped due to notching with semicircular areas of decreased density. Similar changes are present on the mesial surfaces of the distal ends of the first phalanges of the halluces. In the proliferative changes described in the heads of the first metatarsal bones are small, more or less circular areas of decreased density. Two similar areas are found in the head of the fifth metatarsal bone of the left foot.

#### SUMMARY OF ROENTGENOGRAPHIC FINDINGS

More or less generalized bony atrophy occurs. There is a small amount of proliferative changes. One joint space is obliterated with irregularity of the joint surfaces. Most of the joints appear normal. Focal areas of decreased density are found. Nodular thickening of the soft tissues is present.

CASE 7 (Med. No. 6154).—F. J. S., white, male, aged 43 years.

Diagnosis: Gout; obesity.

The patient's habits were good. During the previous ten years he had had numerous attacks of arthritis in one or several joints of the lower extremities. Physical examination was essentially negative. There were no signs of cardiovascular disease. Blood pressure was 130 mm. systolic and 90 mm. diastolic. A tophus was present in the right ear and from it sodium urate crystals were obtained. The urine contained a scant trace of albumin, but no other pathologic elements were found. Phenolsulphonephthalein excretion was 50 per cent. in two hours. The uric acid was 5 mg. and the non-protein nitrogen 44 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 9454).—Hands and wrists: There are no bony changes.

Knees: Both patellae and the external tuberosities of the tibiae show proliferative changes.

Feet: There are slight proliferative changes of the margins of the articular surfaces of the bones forming the metatarsophalangeal joints of both halluces. All other joints are normal. The head of the left first metatarsal bone shows a localized area of decreased density in its mesial portion. The area is figure 8 shaped. Its long diameter is 12 mm. Its borders are only fairly well defined. There is hallux valgus and pes equinus.

#### SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Slight proliferative changes affect the bones of the first metatarsophalangeal joints. A focal area of decreased density is found in the head of the left first metatarsal bone.

CASE 8 (Med. No. 10814).—P. A., white, male, aged 49 years.

Diagnosis: Gout.

The patient drank considerable quantities of wine. For the past eighteen years he had had one or two attacks typical of podagra every year. He was admitted to the hospital during the subsidence of an attack. On physical examination two small tophi were found in the auricle of the right ear. Sodium

urate crystals were obtained from them. There was some periarticular swelling and redness about the metatarsophalangeal joint of the right hallux. Otherwise the physical examination was essentially negative. The urine contained a slight trace of albumin and a variable number of casts. Phenolsulphone-phthalein excretion was 38 per cent. in two hours. There were 6 mg. of uric acid per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 14570).—Feet: There is slight narrowing of the metatarsophalangeal joint of the right great toe. There are slight proliferative changes of the margins of the articular surface of the phalanx entering into this joint. There are proliferative changes about a sesamoid bone just internal to the head of this metatarsal. All other bones and joints are normal. The head of the first metatarsal bone of the right foot on the mesial surface shows two small, well defined semicircular areas of decreased density about 3 mm. in diameter.

#### SUMMARY OF ROENTGENOGRAPHIC FINDINGS

There are slight proliferative changes and focal areas of decreased density in the head of the first metatarsal bone of the right foot.

CASE 9 (Med. No. 10684).—W. C. B., white, male, aged 61 years.

Diagnosis: Gout; chronic nephritis.

The patient's habits were good. For the past ten years he had had attacks of arthritis affecting the ankle joints, tarsal joints and at times the knees. Pain was present but resembled that of acute articular rheumatism rather than that of gout. He was admitted to the hospital with an arthritis of the left knee and right ankle. On physical examination small tophi were found in the auricles of the ears. From them sodium urate crystals were obtained. The heart was moderately enlarged to the left. The radial arteries were sclerosed. Blood pressure was 200 mm. systolic and 115 mm. diastolic. There was some swelling and tenderness of the left knee and right ankle. The urine contained a trace of albumin and a variable number of cases and leukocytes. Phthalein excretion rose from 5 per cent. in two hours to 14 per cent. during the patient's stay in the hospital. The blood urea nitrogen dropped correspondingly from 74 mg. to 56 mg. per 100 c.c. of blood. Uric acid was 8 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 14369).—Knee: No abnormalities are found.

Feet: The heads of both first metatarsal bones and the first phalanx of the left hallux show small circular areas of bony absorption, from 1 to 2 mm. in diameter. The inner surface of the head of the left first metatarsal bone presents a mottled appearance. There is thickening of the soft tissues overlying the metatarsophalangeal joint of the left foot. No joint changes are present.

#### SUMMARY OF ROENTGENOGRAPHIC FINDINGS

Focal areas of decreased density occur in the heads of the first metatarsal bones.

CASE 10 (Med. No. 10638).—A. S., white, female, aged 39 years.

Diagnosis: Gout, chronic nephritis, aortic insufficiency.

The patient had been a moderate user of alcoholic drinks. For the past five years she had had monoarticular and polyarticular attacks of arthritis characterized by great swellings, redness, exquisite tenderness and extreme pain of the affected joints. On physical examination small tophi were found in the auricles of the ears. From them sodium urate crystals were obtained. The heart was enlarged to the left. A diastolic murmur was heard loudest along the left sternal margin. The radial arterial walls were sclerosed. Blood pressure was 218 mm. systolic and 134 mm. diastolic. The metatarsophalangeal joints of both great toes were moderately enlarged. Otherwise the physical examination was essentially negative. The urine contained macro-

scopic blood due to menorrhagia and much albumin. The microscopic examination showed a variable number of hyaline casts. Phenolsulphonephthalein excretion was 36 per cent. in two hours. Nonprotein nitrogen was 53 mg. and uric acid 4 mg. per 100 c.c. of blood. The Wassermann reaction in the blood serum was negative.

*Roentgen Report* (No. 14154).—Hands and wrists: The bones of the hands and wrists are normal.

Feet: The bones of the ankle joints and of the tarsi are normal. The heads of both first metatarsal bones show small, fairly well defined, circular areas of decreased density. Otherwise there are no abnormal findings.

#### SUMMARY OF ROENTGENOGRAPHIC FINDINGS

There are focal areas of decreased density in the heads of the first metatarsal bones.

#### DISCUSSION

Since the tophus is the only universally accepted pathognomonic sign of gout, for studies of that disease only those patients should be chosen in whom tophi are found and sodium urate crystals from them microscopically demonstrated. For this reason only those in which these requisities were fulfilled have been reported in the above protocols. A perusal of the protocols shows that in all cases the focal areas of decreased density which roentgenologists have considered as peculiar to gout were found. Similar changes were present in two other cases which were clinically gout, but in which no tophi were demonstrated. In another case without tophi, but which was clinically gout, the focal areas of decreased bony density were not found. The findings show that these areas are usually present in the bones of the wrists, hands, ankles or feet in gouty subjects.

Strangeways<sup>4</sup> has reported the finding of sodium urate in areas of decreased density which were demonstrated in the roentgenograms of the phalanges of gouty subjects. The roentgenographic appearance of the areas of decreased density as described by this writer show a complete absorption of lime salts and consequently are transparent. Similar areas are described in certain of the cases here reported and are most marked in Cases 2 and 3 (see Case Reports and Figs. 3 and 4). Strangeways also reported the findings of these transparent areas in cases which were typically "rheumatoid arthritis." All subsequent writers have apparently overlooked the work of Strangeways. They have assumed that the focal areas of rarefaction, the so-called gouty bony changes, were always due to the presence of tophi in the bones, and that they were diagnostic of gout. But these writers drew their conclusions from the study of the roentgen-ray findings in patients in many of whom tophi were not found. This detracts somewhat from the certainty that their cases were really gout. That these changes are always the result of tophaceous deposits may be questioned. As an indirect method of attacking the problem we examined the roentgen-

ograms of the bones of the wrists and hands, or the ankles and feet, or of all these regions in one hundred cases of chronic arthritis. These cases had not been diagnosed clinically as gout. They were chosen at random from the files of the roentgenographic department. In thirteen of these one hundred cases the focal areas of decreased density, the so-called gouty bony changes, were found and were fully as well defined as in the cases of true gout. Of the thirteen cases nine had been studied in the wards of the Peter Bent Brigham Hospital, one in private practice and three in the outdoor department of this hospital. In the first ten of these extensive clinical studies had been made and no clinical evidences of gout had been found. The findings are exemplified in Case 1. In three of the cases the amount of uric acid in the blood was determined and was not found to be increased above the normal. In six of the one hundred cases of chronic arthritis focal bony changes more or less closely resembling the focal areas of decreased density found in gout were demonstrated. These focal bony changes were differentiated from those occurring in true gout in that the degree of bony rarefaction was less complete, or the areas were less regular in outline, or their borders were less well defined. One of these cases had been studied in the hospital wards and the remainder in the outdoor department. In two of the one hundred cases of chronic arthritis focal areas of decreased density very irregular in outline or occurring in joint areas showing extensive bony destruction were found. One of these cases had been studied in the wards of the hospital.

These findings show that there are different types of focal areas apparently due to bony rarefaction in the radiograms of the anatomical parts examined in cases of chronic arthritis. Judging from their roentgenographic appearances there is no reason to believe that the factors producing the focal areas of bony rarefaction occurring in those cases are different from those occurring in cases of true gout. One plausible explanation for the production of certain of these bony changes is based on the work of Nichols and Richardson.<sup>6</sup> These investigators have shown that the inorganic salts may be absorbed from bone so as to produce changes detected by the roentgen ray which may not be obvious either macroscopically or microscopically. Focal areas of absorption of this character could produce the changes like those heretofore considered as resulting from the presence of tophi in the bones. That this is probably the explanation for the occurrence of many of these bony changes is indicated by the fact that we have been able to demonstrate the different types of these areas of focal absorption already described.

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6. Nichols, E. H., and Richardson, F. L.: *Arthritis Deformans*, J. M. Res. **21**:149, 1909.

These areas appear to be but different degrees of the same process. Furthermore, a certain number of these areas occur within proliferative or destructive bony changes. Another factor that may play a rôle in the production of the focal areas of decreased density is that of pressure. These areas are often found in regions, such as the inner surfaces of the heads of the first metatarsal bones, which are subjected to pressure; or they may underlie large tophaceous deposits in the soft tissues. Our findings show that the focal areas of decreased density occur in from 10 to 12 per cent. of the cases of chronic arthritis which clinically are not gout. It should be noted that in many of these cases plates of both hands and feet were not available for examination. It is therefore probable that the changes are even more frequent than our figures show. If these changes are the result of tophi in the bones, then gout is far more frequent in its occurrence than heretofore has been suspected. Clinically, such frequency of the disease seems very improbable. These findings show that the focal areas of decreased density, the so-called gouty bony changes, found in the roentgenogram are most probably often not the result of tophi in the bones, but are frequently due to focal absorption of lime salts.

In one of our cases (Case 3) pus and sodium urate crystals could be expressed from a fistula in the little finger of the right hand. This fistula apparently connected with the area of bony absorption described in the two terminal phalanges of that finger. The area of absorption may have been due to urate deposits or it may have been the result of an osteomyelitis. The sodium urate crystals obtained from the fistula could either have come from a tophus in the bone or from tophi in the soft tissue through which it passed. In the middle phalanx of the little finger was a perfectly circular area of complete bony absorption, 4 mm. in diameter. This area may have represented a tophus. However, an area appearing exactly similar, except that it occurred in the edge of a metatarsal bone and hence was semicircular in outline, was found in a case without any clinical evidence of gout. These findings, together with those of Strangeways, seem to rule out the possibility of diagnosing tophi in the bones from the roentgenogram. In any event the areas of decreased density, the transparent areas of Strangeways, are of doubtful aid in diagnosing gout, unless the present clinical conception of that disease be changed radically.

Although the focal areas of decreased density found in gout occur in the other arthritides they are not wholly without diagnostic significance. They were present in the eighteen cases in which plates of both hands and feet were examined in the reports of Drinberg and Jacobsohn. These cases were clinically gout, although tophi were demonstrated in but three of them. If the three of our cases without

tophi are considered as true gout, then all but one of the cases here reported showed the focal areas of bony rarefaction, the so-called gouty changes. If only those cases in which tophi were demonstrated are to be accepted as true gout, then all the cases so far reported, including our own, in which there were roentgenograms of both hands and feet available for examination have shown the changes. Our one case without tophi in which the bony changes did not occur had an attack of podagra while under observation. The blood uric was persistently high and the nonprotein nitrogen within normal limits. Therefore, this case was probably one of gout. The findings of other observers together with our own show that the focal areas of decreased density, heretofore considered as peculiar to gout, are rarely absent in that disease. Their absence would be some evidence against the existence of gout in a given case. On the other hand their presence is no more than suggestive of gout, since they are found in from 10 to 12 per cent. of cases which clinically are not gout.

Strangeways found a type of nongouty arthritis in which the roentgenographic changes exactly corresponded to those of gouty arthritis. Other investigators have paid but scant attention to the type of arthritis occurring in gout. A perusal of the roentgenographic findings in the case reports here presented shows that a variety of radiographic changes are found in the bones and joints of the hands and feet of gouty subjects. These changes may be divided into the four following groups which more or less overlap each other.

1. The focal areas of decreased density may be the only changes found (Case 10). These changes are usually most pronounced in the heads of the metacarpal or metatarsal bones.

2. Besides the focal changes just mentioned very slight lipping at the margins of the articular surfaces of the bones entering into the first metatarsophalangeal joint occurs (Cases 7 and 8).

3. In addition to the changes noted above either a variable degree of atrophy of all the bones of the affected member occurs (Case 5) or largely of only the bones of an involved joint (Case 6).

4. In addition to all the above changes narrowing of certain joint spaces with marked proliferative and atrophic changes occur (Case 2; Fig. 3).

A striking peculiarity of the arthritis is that only certain joints are affected while others remain normal (Cases 2, 3, 4, 5, 6, 7 and 8). The one exception to this statement is found in the feet of Case 2. Here, although all the joints are involved, some are but little affected. A second characteristic is that where there are marked changes in a joint the bones entering into its formation show atrophy (Cases 2, 3, 4, 5 and 6). This atrophy may be limited to these bones, or it may be

generalized in the member affected. The cause for bony atrophy, when present, is somewhat problematical. It may have been due in part to the pressure of the large tophaceous areas in some cases (Cases 2, 3, 5 and 6). It may have been the result of the lack of use of the affected members, the so-called atrophy of disuse. These two characteristics are not mentioned by Strangeways in his report. However, judging from the plates accompanying his article they were present. A third characteristic is that in the seven cases in which arthritis was present one or both metatarsophalangeal joints of the great toes were involved in all but one case (Case 4). In this case questionable lipping at the margins of the articular surfaces of the heads of both first metatarsal bones was present. Hallux valgus occurred in two of these cases (Cases 2 and 7), and was present to a slight extent in one great toe of a third (Case 6). This may explain the arthritis in these three cases. In the other four cases no cause except that of an arthritis due to gout was evident. It should be emphasized that this region of the foot is subject to more or less trauma, but the rôle it played in producing the arthritis cannot be ascertained. On the other hand, this is the most frequent region in which attacks of gouty arthritis occur. A striking feature of the arthritis in the five cases showing the most marked changes was the almost invariable symmetry in the two hands or feet of the bones and joints affected. The so-called Bruce's nodes are well shown in one case (Case 2; Fig. 3). Strangeways has demonstrated that these nodes are bony exostoses and not sodium urate deposits. They are not diagnostic of gout. The most extensive bony and joint changes were present in the case (Case 2) in which gouty attacks had occurred over the longest period of years. This relation between time and the extent of these changes was not present in the other cases.

A comparison of the different types of gouty and nongouty arthritis is instructive. The bony and joint changes in radiograms of the nongouty arthritides very largely fall into the three following classes:

1. A class characterized by proliferative changes at the margins of the articulating surfaces of the bones and a negligible amount of bony atrophy. In radiographic literature this class is called hypertrophic arthritis.

2. A class characterized by generalized bony atrophy without destructive changes of the joint surfaces. No proliferative bony changes occur. There is fusiform thickening of the soft tissues about the joints. Roentgenologists designate this class as atrophic arthritis.

3. A class characterized by proliferative and marked atrophic bony changes. This type of arthritis is the one accompanying demonstrable infections of the joints. It is known as the infectious type of arthritis in roentgen-ray literature.

Focal areas of decreased density, resembling those found in gout, occur in all types of nongouty arthritis. But focal areas of decreased density without any other bony or joint changes have been found only in gout. This may be because of the lack of material for examination, since relatively few cases of early nongouty arthritis have been available for examination. The second gouty group resembles the hypertrophic type of nongouty arthritis. The third and especially the fourth groups fall into a peculiar class. In character their changes resemble the infectious type of nongouty arthritis. In the actual appearances in the roentgenograms, however, a striking difference between the two types of arthritis is usually manifest. This is because of the sharply localized, extreme degree of bony atrophy which occurs in the infectious type of nongouty arthritis. However, of the latter type roentgenograms have been found which closely resemble the atrophic and proliferative changes occurring in gout. One of these cases (J. O., Med. No. 11125) was studied in the hospital wards. Although particularly sought for, no clinical evidences of gout were found. The blood uric acid was 1.3 mg. per 100 c.c. of blood. From the above discussion together with the results of Strangeway's investigations, it is evident that there are no bony or arthritic changes in the roentgenograms which are diagnostic of gout.

#### SUMMARY AND CONCLUSIONS

The findings in the work here reported show that a type of arthritis may occur in gout which presents an unusual appearance in the roentgenogram. Nevertheless, roentgenographic findings in even the most characteristic type of gouty arthritis may be resembled so closely by nongouty arthritis that such findings cannot be considered as more than suggestive of the diagnosis of gout. The focal areas of decreased density in the roentgenogram which roentgenographers consider to be due to tophi are probably very often merely focal areas of absorption of lime salts. These focal areas are found in from 10 to 12 per cent. of the nongouty arthritides and are, therefore, not diagnostic of gout. Their absence is of more diagnostic value than their presence, since they are almost invariably found in some of the bones of the wrists, hands, ankles or feet in true gout.

We wish to thank Dr. G. W. Holmes, chief of the Roentgenographic Department of the Massachusetts General Hospital, Boston, for criticisms and suggestions.

## CORRECTIONS IN ARTICLE ON SINO-ATRIAL BLOCK

*To the Editor:*—In the article on "Sino-Atrial Heart Block in a Child," Arch. Int. Med. **24**:458 (Oct.) 1919, there has been an error in the order of the figures. On page 465 the upper of the three cuts should be the lower and belongs with the legend of Figure 14. The middle cut of the three should be the upper and belongs with the legend of Figure 12. The lower cut should be in the middle and belongs with the legend of Figure 13.

On page 467 there are additional errors which will result in much confusion unless the reader appreciates the fact that the references to illustrations are incorrect.

Page 467, Line 16: "Fig. 11" should come after "four blocks occur in succession."

Line 17: "Fig. 11" should read "Fig. 12."

Line 18: "Fig. 12" should read "Fig. 13."

Line 26: "Fig. 13" should read "Fig. 14."

Line 33: "Fig. 14" should read "Fig. 15."

Line 49: "Figs. 15 and 16" should read "Figs. 16 and 17."

N. WORTH BROWN, Toledo, Ohio.

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The American Medical Association will pay 50 cents each for the following issues of the Archives of Internal Medicine: January, March, June and August, 1918. January and July, 1916; November, 1915; January, 1911; July, 1909. Address to AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.

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## BOTULISM

A STUDY OF THE RESISTANCE OF THE SPORES OF *BACILLUS BOTULINUS* TO VARIOUS STERILIZING AGENCIES WHICH ARE COMMONLY EMPLOYED IN THE CANNING OF FRUITS AND VEGETABLES \*

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AND

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SAN FRANCISCO

In view of the increasing frequency with which, during recent years, it has been shown that outbreaks of food poisoning affecting human beings and domestic animals or fowl have been caused by the ingestion of *B. botulinus* toxin in canned foods, it was considered advisable to make an investigation of the resistance of the spores of *B. botulinus* to various sterilizing agencies which are commonly employed in canning foods. Our interest in the problem was stimulated by the fact that in our investigations of a number of outbreaks of fatal poisoning which had occurred on the Pacific Coast,<sup>1, 2</sup> it was found that practically all had been caused by the ingestion of home canned vegetables and fruits; and in investigating the methods of canning which had been employed in preserving the food it was found that no one method was at fault. Our investigations showed that foods which had been canned by the one period sterilization process, with or without the addition of lemon juice, by the fractional method of sterilization or by a combination of the hot pack and cold pack processes had all, in certain instances, contained a potent toxin of *B. botulinus*. It is unfortunate that in many instances the persons who canned the food

\*From the Laboratory of Experimental Medicine, Leland Stanford Junior University School of Medicine.

\*Aided by a grant from the California State Council of Defense.

\*The experiments described in this paper were performed during the year 1917-1918, but on account of war conditions it was not possible to publish the results at that time.

1. Dickson, E. C.: Botulism. A Clinical and Experimental Study, Monographs of the Rockefeller Institute for Medical Research, No. 8.

2. Dickson, E. C.: Botulism. A Further Report of Cases Occurring in the Pacific Coast States, Arch. Int. Med. **22**:483 (Oct.) 1918.

were victims who succumbed to the poisoning, and it was impossible to obtain exact data as to the canning methods employed, but in other instances we were able to learn the exact procedure in all its detail and to verify by laboratory tests that if the spores of *B. botulinus* were added to the raw material the methods were not efficient to the extent that they destroyed the spores.

Our experiments were performed with the hope that we might learn something of the reason why these various methods of canning may be inefficient, and thereby be able to devise some alterations which might render them efficient under all conditions. It must be admitted that up to the present time our results have not led to the evolution of safer methods, but it must be emphasized that it has not been our purpose merely to accumulate data which may be used for destructive propaganda, but that we have attempted to ascertain the facts which it is essential to recognize if we are to hope to be able to control food poisoning of this type.

The experiments may be divided roughly into two groups: (a) experiments to test the degree of resistance of the spores of *B. botulinus* to various sterilizing agencies, such as exposure to heat or to the action of dilute acid (lemon juice) or sugar at varying temperatures or in varying concentrations; and (b) tests of various methods of canning vegetables or fruits which we had contaminated with the spores of *B. botulinus*; but in several instances we have described experiments of each group under a single subheading for greater convenience in description. In all our experiments we made careful controls and deduced our conclusions only after repeated observations had been made.<sup>3</sup>

*A. Experiments to determine the thermal death point of spores of B. botulinus under conditions analogous to those which obtain when they are mixed with food material.*

The spores of eight strains of *B. botulinus* were used in these experiments, Strains I and II, which are old laboratory stock cultures, III, V and VIII, which we isolated from spoiled home canned string beans, VI (the Niven strain), which was recovered from cheese, VII, which we obtained from spoiled home canned asparagus, and IV, which we recovered from home canned corn. Strains III, IV, V, VI and VII were recovered from food which had produced fatal poisoning of human beings, and strain VIII from material which had poisoned a number of chickens. With the exception of strains I, II and V, all produce a highly potent toxin when grown on suitable

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3. These investigations have been carried further by one of us and some of the later observations have already been published. Burke, G. S.: The Effect of Heat on the Spores of *Bacillus botulinus*, J. A. M. A. **72**:88 (Jan. 11) 1919.

culture mediums. The spores were obtained in strains I to VII, inclusive, by incubating the respective strains in brain medium at 26 C. for at least six weeks, and in strain VIII from a jar of string beans which had been canned by Mrs. M. at Berkeley, Calif. (2. Sect. B. Outbreak 1). The brain mediums and the beans were thoroughly mashed and diluted with normal salt solution to a fluid consistency. By this procedure we obtained an admixture of spores and animal or vegetable protein, an intimate association simulating that which exists when food material is contaminated with spores.

#### TECHNIC

Ten c.c. of each spore bearing mixture was placed in thin glass test tubes which were immersed into water in a water bath in such a manner that the surface of the fluid in the tubes was at least two inches below the surface of the water. A constant temperature was maintained at the degree required in each experiment, and test inoculations were made from each tube every fifteen minutes, the portion for inoculation being removed by a glass pipet which had been heated to the temperature of the contents of the tube, and transferred to freshly boiled deep glucose agar tubes. The culture tubes were sealed with wax to prevent drying, and were incubated at 26 C. They were examined daily for two weeks, after which, if there was no visible growth, they were discarded. The results of the experiments<sup>4</sup> are shown in Tables 1, 2 and 3.

The results obtained in these experiments are of considerable interest because of the demonstration that, when mixed with an animal or a vegetable protein, the spores of *B. botulinus* are extremely resistant to heat. This observation is entirely at variance with the statement which is found in all the textbooks, where the thermal death point of the spores of this bacillus is given at exposure to 80 C. for one hour. The fact that all the strains survived after being heated at 90 C. for three hours, that seven survived after being heated at 95 C. for three hours, and that six survived immersion in boiling water for two hours is ample proof that we are not dealing with a purely accidental observation. The significance of this high resistance, in so far as the canning of foods is concerned, will be considered under another section.

B. *Experiments to test the value of the addition of acid (lemon juice) to vegetables in so far as inhibiting the growth of B. botulinus is concerned.*

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4. In the later experiments described by Mrs. Burke it was found that after being heated the spores sometimes remain quiescent for considerably longer than two weeks, hence in the present experiments it is possible that a larger percentage of positive subcultures would have been obtained had we not discarded our tubes in two weeks.

TABLE 1.—SHOWING THE EFFECT WHEN SPORES OF *B. BOTULINUS* MIXED WITH ANIMAL OR VEGETABLE PROTEIN ARE IMMERSSED IN WATER AT 90 C. FOR THREE HOURS

Inoculation Time	Strain							
	I	II	III	IV	V	VI	VII	VIII
Control*	1 day	1 day	3 days	3 days	1 day	4 days	1 day	3 days
15 minutes	1 day	1 day	4 days	3 days	1 day	3 days	—	5 days
30 minutes	1 day	1 day	3 days	3 days	1 day	4 days	7 days	4 days
45 minutes	2 days	1 day	3 days	3 days	2 days	4 days	7 days	8 days
60 minutes	1 day	1 day	3 days	4 days	1 day	3 days	—	9 days
75 minutes	2 days	1 day	4 days	4 days	2 days	3 days	—	8 days
90 minutes	1 day	1 day	4 days	5 days	1 day	3 days	—	8 days
105 minutes	2 days	1 day	4 days	5 days	2 days	3 days	—	10 days
120 minutes	1 day	1 day	3 days	5 days	1 day	3 days	6 days	8 days
135 minutes	2 days	1 day	4 days	8 days	1 day	3 days	—	—
150 minutes	2 days	2 days	5 days	5 days	2 days	4 days	10 days	—
165 minutes	2 days	2 days	5 days	5 days	2 days	4 days	10 days	—
180 minutes	2 days	2 days	5 days	5 days	2 days	3 days	3 days	11 days

\* The control inoculations were made as soon as the contents of the tubes had risen to that of the surrounding water. The spores of Strains I to VII inclusive were mixed with brain medium, those of Strain VIII with crushed canned string beans.

The number of the days recorded is that on which the characteristic growth with fragmentation of the medium by gas was first observed.

TABLE 2.—SHOWING THE EFFECT WHEN SPORES OF *B. BOTULINUS* MIXED WITH ANIMAL OR VEGETABLE PROTEIN ARE IMMERSSED IN WATER AT 95 C. FOR THREE HOURS

Inoculation Time	Strain							
	I	II	III	IV	V	VI	VII	VIII
Control	1 day	1 day	1 day	2 days	1 day	1 day	2 days	2 days
15 minutes	1 day	1 day	3 days	2 days	1 day	1 day	2 days	2 days
30 minutes	1 day	2 days	3 days	3 days	2 days	2 days	3 days	4 days
45 minutes	2 days	2 days	5 days	3 days	2 days	2 days	5 days	4 days
60 minutes	2 days	2 days	6 days	4 days	2 days	2 days	5 days	5 days
75 minutes	2 days	2 days	10 days	4 days	2 days	2 days	6 days	3 days
90 minutes	2 days	2 days	11 days	4 days	2 days	2 days	6 days	4 days
105 minutes	3 days	2 days	11 days	5 days	2 days	2 days	6 days	5 days
120 minutes	3 days	2 days	—	6 days	2 days	2 days	6 days	4 days
135 minutes	4 days	3 days	—	—	3 days	3 days	7 days	8 days
150 minutes	5 days	2 days	—	—	3 days	3 days	7 days	4 days
165 minutes	3 days	3 days	—	8 days	3 days	3 days	8 days	6 days
180 minutes	2 days	2 days	—	—	4 days	3 days	7 days	12 days

TABLE 3.—SHOWING THE EFFECT WHEN SPORES OF *B. BOTULINUS* MIXED WITH ANIMAL OR VEGETABLE PROTEIN ARE IMMERSSED IN BOILING WATER FOR TWO HOURS

Inoculation Time	Strain							
	I	II	III	IV	V	VI	VII	VIII
Control	1 day	1 day	3 days	1 day	1 day	1 day	2 days	3 days
15 minutes	2 days	2 days	5 days	3 days	2 days	2 days	4 days	5 days
30 minutes	2 days	3 days	6 days	5 days	2 days	2 days	4 days	9 days
45 minutes	2 days	3 days	8 days	4 days	2 days	3 days	—	5 days
60 minutes	3 days	7 days	10 days	6 days	7 days	4 days	5 days	5 days
75 minutes	2 days	—	10 days	—	2 days	2 days	6 days	5 days
90 minutes	3 days	—	—	—	2 days	2 days	7 days	5 days
105 minutes	4 days	—	—	4 days	6 days	2 days	8 days	5 days
120 minutes	13 days	—	—	4 days	2 days	2 days	13 days	11 days

In Circular No. 158 of the University of California Agricultural Experimental Station, W. V. Cruess describes a modification of the one period method of sterilization which "consists essentially of making the vegetables slightly acid, thus rendering them as easy to sterilize as fruits." In discussing his method on page 4 of the circular, Cruess writes: "It was found that peas heated to 212 F. in a brine acidified by the addition of five ounces of lemon juice to every gallon kept perfectly, while peas heated in the same brine, without the lemon juice, spoiled. The same results were obtained with beans, pumpkins, beets, turnips, artichokes and asparagus."

Three sets of experiments were undertaken:

1. To test whether lemon juice in the concentration recommended by Cruess will of itself inhibit the growth and toxin formation of *B. botulinus*;

2. To test whether varying concentrations of lemon juice will lower the thermal death point of spores of *B. botulinus*; and

3. To test whether the actual method of canning which Cruess recommends is efficient if the raw material is contaminated with spores of *B. botulinus*.

1. EXPERIMENTS TO TEST WHETHER LEMON JUICE BRINE IN THE CONCENTRATION RECOMMENDED BY CRUESS WILL INHIBIT THE GROWTH AND TOXIN FORMATION OF *B. BOTULINUS*.

*Technic.*—Beef infusion broth was prepared according to the formula recommended by van Ermengem,<sup>5</sup> and sufficient quantities of salt, sugar and lemon juice were added to make up acid broth brines of the same concentration as Cruess recommends for green peas and string beans respectively. (Peas:  $2\frac{1}{3}$  ounces salt,  $3\frac{1}{2}$  ounces sugar and 7 ounces lemon juice per gallon; Beans:  $2\frac{1}{2}$  ounces salt, 5 ounces sugar and 5 ounces lemon juice per gallon). The medium was thoroughly boiled and cooled, inoculated with washed bacilli (*B. botulinus*, strain III) and covered with liquid petrolatum. Control tubes of plain van Ermengem broth were prepared and inoculated, and all the tubes were incubated at 26 C. for about six weeks. Subcultures were then made to demonstrate the presence of living bacteria, and after filtration through diatomaceous filters, the lemon juice-brine broth was tested for the presence of toxin. Guinea-pigs weighing from 200 to 275 gm. were used for the inoculations. The results of the experiment are tabulated in Table 4.

The experiment shows that lemon juice brine, in the concentration recommended by Cruess for peas and beans, does not prevent the

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5. Van Ermengem, E.: Der Bacillus botulinus und der Botulismus: in Kolle, W., and von Wassermann, A., Handbuch der pathogenen Mikroorganismen, Jena, Ed. 2, 4:909, 1912.

growth of *B. botulinus* nor the development of the toxin, notwithstanding the fact that the optimum reaction for the development of botulinus toxin is neutral or slightly alkaline. However, the amount of toxin developed in both brines was considerably less than occurred in the control van Ermengem broth.

TABLE 4.—SHOWING THE EFFECT ON THE GROWTH AND TOXIN FORMATION WHEN *B. BOTULINUS* IS INCUBATED IN LEMON JUICE BRINE-BROTH

Mediums*	Bacteria Recovered	Toxin Tests				
		Animals Died in				
		1 C.c.	0.5 C.c.	0.002 C.c.	0.001 C.c.	0.0005 C.c.
Control broth.....	Yes	—	—	—	—	48 hours
Peas brine.....	Yes	16 hours	16 hours	21 hours	Survived	Survived
Beans brine.....	Yes	16 hours	16 hours	21 hours	Survived	Survived

\* The brine-broths contain the concentrations of lemon juice and salt which Cruess recommends for canning peas and beans respectively.

## 2. EXPERIMENTS TO TEST THE EFFECT OF VARIOUS CONCENTRATIONS OF LEMON JUICE ON THE THERMAL DEATH POINT OF SPORES OF *B. BOTULINUS*.

*Technic.*—To a series of test tubes containing each 10 c.c. of a diluted brain medium culture of *B. botulinus* (strain III) in which were numerous spores, sufficient lemon juice was added to make a concentration of 25, 12.5, 6.25, 3.12 and 1.56 per cent. lemon juice respectively. These tubes, together with a control tube to which no lemon juice had been added, were immersed in a water bath (as in experiments described in A) which was kept at a constant temperature of 80, 90, 95 and 100 C., respectively, during the various investigations. Beginning with the time at which the mixture in the tubes had reached the temperature of the surrounding water, and at fifteen minute intervals thereafter throughout the experiments, test inoculations were made into deep glucose agar, as in section A. The subcultures were examined daily for the appearance of visible growth and fragmentation of the medium, but when still negative on the sixteenth day they were discarded. The results of the experiments are tabulated in Tables 5, 6, 7 and 8.

The experiments show that the addition of lemon juice to a mixture of spores of *B. botulinus* in brain medium, i. e., animal protein, has a very definite effect in lowering the thermal death point of the spores. In Table 5, where the mixtures were submitted to a temperature of 80 C., although the spores survived for three hours in all concentrations of lemon juice, there was a definite and progressive delay in growth after heating in the higher concentrations of lemon juice, probably indicating that the spores were damaged although not killed. In Tables 6, 7 and 8, where the mixtures were submitted to temperatures of 90, 95 and 100 C., respectively, there was indication that the

TABLE 5.—SHOWING THE EFFECT OF SUBMITTING SPORES OF *B. BOTULINUS* WHICH ARE MIXED WITH ANIMAL PROTEIN, AND IN THE PRESENCE OF VARYING CONCENTRATIONS OF LEMON JUICE, TO A TEMPERATURE OF 80 C.

Time of Inoculation	Percentage Lemon Juice					
	25 per Cent.	12.5 per Cent.	6.25 per Cent.	3.12 per Cent.	1.56 per Cent.	n/salt
Control	3 days*	3 days	3 days	3 days	3 days	3 days
Heated						
15 minutes	6 days	3 days	3 days	3 days	3 days	3 days
30 minutes	6 days	4 days	3 days	3 days	3 days	3 days
45 minutes	6 days	4 days	3 days	3 days	3 days	3 days
60 minutes	8 days	4 days	3 days	3 days	3 days	3 days
75 minutes	9 days	4 days	3 days	3 days	3 days	3 days
90 minutes	10 days	6 days	3 days	3 days	3 days	3 days
105 minutes	10 days	6 days	3 days	3 days	3 days	3 days
120 minutes	6 days	6 days	3 days	3 days	3 days	3 days
135 minutes	16 days	8 days	3 days	3 days	3 days	3 days
150 minutes	9 days	8 days	3 days	3 days	3 days	3 days
165 minutes	—	8 adys	3 days	3 days	3 days	3 days
180 minutes	10 days	10 days	3 days	3 days	3 days	3 days

\* The number of days indicates, in each case, the time at which visible growth with fragmentation of mediums was first observed.

TABLE 6.—SHOWING THE EFFECT OF SUBMITTING A MIXTURE OF SPORES OF *B. BOTULINUS* IN ANIMAL PROTEIN AND LEMON JUICE TO A TEMPERATURE OF 90 C.

Time of Inoculation	Amount Lemon Juice					
	25 per Cent.	12.5 per Cent.	6.25 per Cent.	3.12 per Cent.	1.56 per Cent.	n/salt
Control	5 days	4 days	4 days	Contam- inated	4 days	4 days
Heated						
15 minutes	N. G.*	N. G.	8 days	4 days	4 days	4 days
30 minutes	N. G.	N. G.	11 days	5 days	4 days	4 days
45 minutes	N. G.	N. G.	N. G.	8 days	4 days	4 days
60 minutes	N. G.	N. G.	N. G.	N. G.	6 days	4 days
75 minutes	N. G.	N. G.	N. G.	N. G.	—	4 days
90 minutes	N. G.	N. G.	N. G.	N. G.	8 days	4 days
105 minutes	N. G.	N. G.	N. G.	N. G.	8 days	4 days
120 minutes	N. G.	N. G.	N. G.	N. G.	10 days	4 days
135 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	4 days
150 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	4 days
165 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	4 days
180 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	4 days

\* N. G. indicates that there was no growth or fragmentation visible in 16 days.

TABLE 7.—SHOWING THE EFFECT OF SUBMITTING A MIXTURE OF *B. BOTULINUS* IN ANIMAL PROTEIN AND LEMON JUICE TO A TEMPERATURE OF 95 C.

Time of Inoculation	Amount Lemon Juice					
	25 per Cent.	12.5 per Cent.	6.25 per Cent.	3.12 per Cent.	1.56 per Cent.	n/salt
Control	6 days	5 days	4 days	3 days	3 days	3 days
15 minutes	N. G.	N. G.	N. G.	9 days	5 days	3 days
30 minutes	N. G.	N. G.	N. G.	9 days	6 days	5 days
45 minutes	N. G.	N. G.	N. G.	N. G.	8 days	5 days
60 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	6 days
75 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	10 days
90 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	10 days
105 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	11 days
120 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	N. G.

higher the concentration of lemon juice the more readily were the spores destroyed, and in the instances where the spores survived, the length of time which elapsed before growth could be observed was roughly dependent on the concentration of the lemon juice, the length of the exposure to heat and the degree of heat.

3. EXPERIMENTS TO TEST THE EFFICIENCY OF THE PROCESS OF CANNING VEGETABLES BY THE ONE PERIOD METHOD OF STERILIZATION AFTER A GIVEN AMOUNT OF LEMON JUICE HAD BEEN ADDED TO THEM (CRUESS METHOD).

String beans and green peas were selected for the experiment and the directions given in the University of California Agricultural Experiment Station Bulletin No. 158, pages 28 and 29, were closely followed.

TABLE 8.—SHOWING THE EFFECT OF SUBMITTING SPORES OF *B. BOTULINUS* IN MIXTURE WITH ANIMAL PROTEIN AND LEMON JUICE TO THE TEMPERATURE OF BOILING WATER

Time of Inoculation	Amount Lemon Juice					
	25 per Cent.	12.5 per Cent.	6.25 per Cent.	3.12 per Cent.	1.56 per Cent.	n/salt
Control	5 days	5 days	3 days	3 days	3 days	3 days
15 minutes	N. G.	N. G.	7 days	6 days	5 days	5 days
30 minutes	N. G.	N. G.	N. G.	N. G.	7 days	6 days
45 minutes	N. G.	N. G.	N. G.	N. G.	12 days	8 days
60 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	10 days
75 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	10 days
90 minutes	N. G.	N. G.	N. G.	N. G.	N. G.	N. G.

(a) *String Beans*.—The beans were washed, broken into pieces about  $1\frac{1}{2}$  inches long, blanched by dipping into boiling water for four minutes, chilled in cold water and packed into one quart Mason jars. During the process of filling the jars about 1 c.c. of a suspension of spores of *B. botulinus* (strain III) in salt solution was placed near the center of the jar. The beans were covered with boiling hot brine containing 2 per cent. salt and lemon juice in the proportion of 5 ounces per gallon, and sterilized covers were loosely applied. The jars were then immersed in boiling water in a wash boiler, and left for ninety minutes after the water recommenced to boil. At the end of the heating process the jars were removed, the covers tightened and the jars were placed in a dark closet.

(b) *Green Peas*.—The peas were shelled, blanched, packed and inoculated with a mixture of spores of *B. botulinus* (strain III) as were the beans, and were covered with a boiling hot brine containing  $2\frac{1}{3}$  ounces of salt,  $3\frac{1}{2}$  ounces of sugar and 7 ounces of lemon juice per gallon. The jars were left immersed in the boiling water in the wash boiler for one hour after the water recommenced to boil. They were then taken out, the covers were tightened and the jars were stored in a dark closet.

(c) *Controls*.—These were prepared by filling jars with blanched string beans in the same way as described in (a) with the exception that boiling water was substituted for the brine, and one teaspoonful of salt was added to each jar. In order that they might serve as a control for the one period cold pack process as well as for the method immediately under observation, the jars were left in the boiling water in the wash boiler for two hours, as recommended on page 17 of the U. S. Department of Agriculture, Farmer's Bulletin No. 839, instead of for ninety minutes as recommended by Cruess. The jars were then stored in a dark closet.

Results: After an interval of one month all the jars were opened. The peas and beans which had been canned by the Cruess method, with lemon juice, showed slight discoloration and one jar contained a mold, but cultures failed to show any growth of *B. botulinus*, and injection experiments failed to demonstrate the presence of toxin.

The contents of the control jars, on the other hand, contained very many spore bearing bacteria which were morphologically and culturally identical with the *B. botulinus* with which the beans had been inoculated, and injection of filtered juice into guinea-pigs demonstrated the presence of a highly virulent toxin.

The experiments indicate, therefore, that the Cruess method of canning vegetables with lemon juice is efficient even if the contents of the jars have been contaminated by spores of *B. botulinus* placed near the center of the jars. The control experiments provide further evidence that the wash boiler method of sterilization applied in the cold pack method of canning vegetables is inefficient under similar conditions.

It should be mentioned, however, that there is one recorded instance of fatal botulism intoxication from string beans which were canned "with some lemon juice," the amount of which could not be ascertained as the woman who canned the beans succumbed to the poisoning. (2. Sect. A, Outbreak 13).

*C. Experiments to test the efficiency of the fractional method of sterilizing vegetables which are contaminated with spores of B. botulinus.*

1. The method of fractional sterilization which was selected for investigation was that described by Breazeale in the U. S. Department of Agriculture Farmers' Bulletin No. 359. String beans were used for the experiment.

The beans were washed, broken into short pieces and packed into one quart jars, 1 c.c. of a mixture of spores of *B. botulinus* (strain III) being placed on the beans near the center of each jar. One level

teaspoonful of salt was added to each jar and cold water was added to fill the jars completely. The tops were applied loosely and the jars were placed in tepid water in a wash boiler which had a tightly fitting cover. The water in the boiler was gradually heated to boiling, and the jars were left in place for a full hour after the water had commenced to boil. The jars were then removed from the wash boiler and the tops were screwed tight. Half of the jars were allowed to remain at room temperature during the periods between sterilization, and the remainder were returned to the covered boiler where they cooled more gradually. On the second and third days the tops of the jars were loosened, and the process of heating was repeated. After the final sterilization, the tops were fastened tightly and the jars were placed in an incubator where they were left for one month in a temperature of 26 C.

When the jars were opened, the appearance of the contents was excellent, the odor was good, aerobic and anaerobic cultures showed no growth and injection of filtered juice with guinea-pigs failed to show the presence of toxin.

It would appear, therefore, that when followed carefully, the fractional method of sterilization in canning vegetables is efficient even though the raw material is contaminated with spores of *B. botulinus*. Attention should be drawn, however, to Case 3 in Section B. of a previous report<sup>2</sup> in which corn which was canned at home by this method contained a toxin which caused the death of a large number of chickens.

2. A second series of experiments was performed to test a method of fractional sterilization which is apparently in common use in certain sections of the country, and which we were requested to test. The method consisted of "blanching and packing vegetables into one quart jars and subjecting the sealed pack to a jumping boil for fifteen minutes on each of three successive days." As was to be expected, it was found that this method is totally inefficient if the raw material is contaminated with spores of *B. botulinus*.

D. *Experiments to test whether the presence of cane sugar in canned fruits will inhibit the growth of B. botulinus and the formation of its toxin.*

In a previous report<sup>1</sup> it was shown that infusions of apricots and peaches form a suitable medium for the growth of *B. botulinus* and for the formation of a virulent toxin, and subsequent experiments have shown that pears and prunes may also be employed in making suitable culture mediums. It became apparent, therefore, that the ordinary methods of canning should be investigated, especially since it is

believed that fruits require much less sterilization because of their acidity and because of the addition of sugar which is supposed to aid in preservation.

1. EXPERIMENTS TO TEST WHETHER CANE SUGAR IN DIFFERENT CONCENTRATIONS WILL PREVENT THE GROWTH AND TOXIN FORMATION OF *B. BOTULINUS*.

Beef broth was prepared according to the formula recommended by van Ermengem<sup>5</sup> with the exception that the 2 per cent. glucose was omitted, and sufficient quantities of cane sugar were substituted to form syrups of 12, 24, 35, 50 and 64 per cent., respectively, which are the concentrations of syrups recommended in the U. S. Department of Agriculture Farmers' Bulletin No. 839, page 14, for canning various fruits. The mediums were boiled and cooled, inoculated with a suspension of spores of *B. botulinus* (strains III and VI) which had been washed thoroughly in successive changes of physiologic solution of sodium chlorid to remove adherent toxin, covered with liquid petrolatum and incubated at 26 C. for one month. At the end of that time, subcultures were made, the syrups were passed through diatomaceous filters, and the filtrates were injected into guinea-pigs to test for the presence of virulent toxin. The results of these experiments are shown in Tables 9 and 10.

TABLE 9.—VALUE OF VARIOUS CONCENTRATIONS OF CANE SUGAR IN PREVENTING THE GROWTH AND FORMATION OF TOXIN OF *B. BOTULINUS* (STRAIN III)

Medium	Time of Growth	<i>B. botulinus</i> Recovered	Demonstration of Toxin	
			Guinea-pig Died In	
			0.5 C.c.	0.002 C.c.
2 per cent. glucose broth (control*)....	1 month	Yes	16 hours	48 hours
12 per cent. cane sugar broth.....	1 month	Yes	16 hours	70 hours
25 per cent. cane sugar broth.....	1 month	Yes	18 hours	70 hours
35 per cent. cane sugar broth.....	1 month	Yes	18 hours	Survived
50 per cent. cane sugar broth.....	1 month	Yes	18 hours	Survived
64 per cent. cane sugar borth.....	1 month	Yes	18 hours	Survived

\* The control glucose broth was of the same lot of broth as the cane sugar broth. Guinea-pigs weighing from 250 to 300 gm. were used in testing for toxin.

TABLE 10.—VALUE OF VARIOUS CONCENTRATIONS OF CANE SUGAR IN PREVENTING THE GROWTH AND FORMATION OF TOXIN OF *B. BOTULINUS* (STRAIN VI)

Medium	Time of Growth	<i>B. botulinus</i> Recovered	Demonstration of Toxin	
			Guinea-pig Died In	
			0.5 C.c.	0.002 C.c.
2 per cent. glucose broth (control)....	1 month	Yes	16 hours	16 hours
12 per cent. cane sugar broth.....	1 month	Yes	16 hours	40 hours
24 per cent. cane sugar broth.....	1 month	Yes	16 hours	4 days
35 per cent. cane sugar broth.....	1 month	Yes	16 hours	40 hours
50 per cent. cane sugar broth.....	1 month	Yes	45 hours	Survived
64 per cent. cane sugar broth.....	1 month	Yes	42 hours	Survived

The experiments show conclusively that cane sugar in concentration up to 64 per cent. does not prevent the growth of *B. botulinus* or the formation of its toxin, although it does inhibit the toxin formation to a certain extent. In Table 9 it is shown that although 35, 50 and 64 per cent. cane sugar broths contain sufficient toxin to kill the guinea-pigs when 0.5 c.c. is injected, there is not sufficient toxin to kill when only 0.002 c.c. is injected; moreover, it is shown that although in 2 per cent. glucose broth culture grown for a similar length of time there is sufficient toxin in 0.002 c.c. to kill a guinea-pig in forty-eight hours, in equal quantities of 12 and 24 per cent. cane sugar broths the amount of toxin present requires seventy hours to cause the death of the animal. Analogous results are shown in Table 10 when strain VI *B. botulinus* was used, although with this strain a more virulent toxin was obtained in 35 per cent. cane sugar broth than was the case with strain III.

2. EXPERIMENTS TO TEST WHETHER FRUITS WHICH HAD BEEN CANNED IN SUGAR FORM A SUITABLE MEDIUM FOR THE GROWTH OF *B. BOTULINUS* AND THE DEVELOPMENT OF ITS TOXIN.

In order that we might have as tests fruit in which there was presumably the optimum concentrations of syrup it was decided to use the highest grade of commercially canned goods which could be obtained in the market. Apricots, peaches and pears were selected, as in previous experiments we had found that infusions prepared from these respective fruits formed suitable mediums for toxin formation.

The tops of the cans were thoroughly washed, dried and burned over with alcohol to ensure sterilization of the surface. Small holes were punched with a sterilized file point, and through the punctures 1 c.c. of a suspension of thoroughly washed spores of *B. botulinus* (strain III) was introduced. The cans were resealed by soldering the punctures and were incubated at 26 C. for about three months. At the end of this time the cans were opened with sterile precautions, subcultures were made to test for the presence of living bacteria, and 1 c.c. of the syrup was injected into guinea-pigs to test for virulent toxin. The results of the experiments are shown in Table 11.

TABLE 11.—FRUITS WHICH HAVE BEEN CANNED IN SUGAR FORM A SUITABLE MEDIUM FOR THE GROWTH OF *B. BOTULINUS* AND THE FORMATION OF ITS TOXIN

Fruit	Time of Growth	Sub-cultures		Toxin in Syrup: Animals Died in
		Aerobic	Anaerobic	
Apricots I.....	3 months	No growth	<i>B. botulinus</i>	2 days
Apricots II.....	3 months	No growth	<i>B. botulinus</i>	2 days
Peaches I.....	3 months	No growth	<i>B. botulinus</i>	2 days
Peaches II.....	3 months	No growth	<i>B. botulinus</i>	1 day
Pears I.....	3 months	No growth	<i>B. botulinus</i>	2 days
Pears II.....	3 months	No growth	<i>B. botulinus</i>	2 days

The experiments show conclusively that apricots, peaches and pears which have been canned in sugar form suitable mediums for the growth of *B. botulinus* and the formation of its toxin, although the amount of toxin is very much less than is found when the organism is grown upon optimum medium.

*E. Experiments to test the efficiency of the cold pack method of canning fruits, with or without the addition of sugar, when the raw material is contaminated with spores of B. botulinus.* The wash boiler method of sterilization was used.

#### 1. FRUITS CANNED WITHOUT SUGAR:

Peaches and prunes were selected for the experiment, and were as fresh as could be obtained in the open market. The fruit was canned according to the instructions given in the U. S. Department of Agriculture Farmers' Bulletin No. 839, page 15.

(a) *Peaches*.—The fruit was washed, pared and halved, the stones being discarded in half the jars and retained in the others, and after rinsing in cold water was packed into heated one quart Mason jars. About 1 c.c. of a suspension of spores of *B. botulinus* (strain III) was placed on the fruit near the center of each jar. The fruit was covered with boiling water, freshly boiled covers were applied and loosely fastened, and the jars were immersed in boiling water in a wash boiler where they were allowed to remain for thirty minutes after the water recommenced to boil. The jars were then removed from the wash boiler, the tops were tightened and the fruit was stored in a dark closet.

(b) *Prunes*.—The method of procedure was the same as that adopted with peaches, except that the fruit was not pared. The stones were removed in one half the jars and retained in the others. The duration of the sterilizing process was thirty minutes.

#### 2. FRUITS CANNED WITH SUGAR:

Peaches and prunes were selected for these experiments also, which were run concurrently with those just described. The instructions given on pages 19 and 20 of Farmers' Bulletin No. 839 were closely followed.

(a) *Peaches*.—The method of preparing, packing and inoculating the fruit was identical with that described in the previous experiment, with the exception that boiling thin syrup, 16 per cent., was substituted for the boiling water. The jars were left immersed in boiling water for sixteen minutes, after which they were removed and stored in a dark closet.

(b) *Prunes*.—The method of procedure was the same as was adopted in the preceding experiment with prunes, except that the fruit

was covered with a medium thick syrup, 45 per cent., instead of with boiling water. The jars were left immersed in boiling water for sixteen minutes.

Results: After two months the jars were opened, aerobic and anaerobic cultures were made to demonstrate the presence of living bacteria, and guinea-pigs were injected to demonstrate the presence of toxin.

From all the jars we obtained pure cultures of *B. botulinus*, although in none of the jars was there toxin in the amount that 1 c.c. of the juice would cause any symptoms when injected into a guinea-pig. The fact that the bacteria had not lost the power of forming toxin was shown, however, by the fact that subcultures from the contents of the jars into glucose broth showed a vigorous growth and a highly potent toxic formation.

The experiments showed, therefore, that the period of sterilization was not sufficient to kill the spores of *B. botulinus*. The significance of the absence of toxin will be discussed later.

#### DISCUSSION

The observations recorded in the foregoing experiments assume considerable importance when we attempt to explain the causes of spoilage and the presence of botulinus toxin in canned vegetables and fruits. The recent noticeable increase in the number of outbreaks of botulinus intoxication<sup>1, 2</sup> in various portions of the United States<sup>6</sup> the great majority of which were caused by the ingestion of canned foods,<sup>7</sup> affords indisputable evidence that methods of canning which have hitherto been considered efficient are not efficient if the raw material happens to be contaminated with spores of *B. botulinus*.<sup>8</sup> It has become apparent from the distribution of outbreaks affecting human beings,<sup>9</sup> as well as from observations of Graham, Brueckner and Pontius<sup>10</sup> in outbreaks of forage poisoning in domestic animals, that the distribution of the *B. botulinus* is widespread throughout the

6. Curfman, G. H.: Botulism, Colorado Med. **15**:35 (Feb.) 1917.

7. McCaskey, G. W.: *Bacillus Botulinus* Poisoning, with a Report of Seven Cases, Four of which Proved Fatal, Am. J. M. Sc. **158**:57 (July) 1919.

8. Thom, C., Edmondson, Ruth B., and Giltner, L. C.: Botulism from Canned Asparagus, J. A. M. A. **73**:907 (Sept. 20) 1919.

9. In addition to the recorded cases we have record of seven more outbreaks occurring in the United States, and one in Yukon Territory in Canada in which human beings were poisoned.

10. Graham, L., Brueckner, A. L., and Pontius, R. L.: Studies in Forage Poisoning, VI, Bull. 208, Kentucky Agricultural Experiment Station. Graham, L., and Brueckner, A. L.: Studies in Forage Poisoning: The Relation of *B. Botulinus* to Forage Poisoning or Cerebrospinal Meningitis in Horses, J. Bacteriol. **4**:1 (Jan.) 1919.

country, and recent observations by one of us<sup>11</sup> give ample proof that the organism occurs in nature under conditions which are ideal for the contamination of foods such as are canned for human consumption.

The observations which were made concerning the thermal death point of spores of *B. botulinus* when mixed with animal or vegetable protein, a state of affairs which simulates that which exists when food materials are contaminated, are most striking. The description of *B. botulinus* which was elaborated by van Ermengem<sup>5</sup> and which has been universally accepted by all the authors of textbooks, states that heating to 80 C. for one hour will effectively destroy the spores, and, as a result, all methods of canning in which the sterilizing process has maintained a temperature which exceeded this have been considered safe in so far as *B. botulinus* is concerned. Our experiments show that the spores under conditions which simulate those which obtain when food material is contaminated will resist the temperature of boiling water for more than two hours, and of 95 C. for more than three hours, a fact that had not previously been suspected. Since it is impossible for the contents of a can or jar to assume a temperature higher than that of the surrounding medium, it is evident that any process of sterilization in which the temperature of boiling water is the highest temperature employed, the length of time necessary to sterilize the most accessible of the contents of the containers must exceed two hours, though how much more we have not yet determined. Moreover, it has been shown by various observers, that it requires an appreciable length of time for the contents at the center of the containers to reach the temperature of the surrounding medium. Bitting and Bitting<sup>12</sup> have studied this problem, and on page 32 of their report state: "The greatest factor affecting under-sterilization is the consistency of the material canned. . . . In experimental work it was found that the heat at the center of a No. 3 can containing water was raised from 85 to 210 F. in about four minutes after being dropped into the boiling water. The sweet potato (pie packed sweet potatoes) may require from three to four hours to reach a temperature above 200 F., and generally does not come within ten degrees of that of the bath during the whole process. In the former case, convection currents are established and the heat is conducted rapidly, in the latter no convection currents are present, and the broken, homogeneous mass acts almost as an insulating material for the central part."

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11. Burke, Georgina S.: The Occurrence of *B. Botulinus* in Nature. In press (J. Bacteriol.).

12. Bitting, A. W., and Bitting, K. G.: Bacteriological Examination of Canned Foods. Research Laboratory National Canners' Association, Bull. No. 14, 1917.

It is evident, therefore, that when we depend upon the temperature of boiling water to effect complete sterilization of the contents of can or jar, we must make allowance for the fact that the contents at the center of the container are much more resistant to sterilization than those at the periphery. If we are to obtain complete sterilization at the center of the jar, it is necessary to leave the jar immersed in boiling water for a considerably longer time than that required to sterilize the contents at the periphery, the extent of the increase depending on the character of the food being canned.<sup>13</sup>

In our experiments with lemon juice the results were instructive in that they show conclusively that when exposed to certain degrees of acidity the spores of *B. botulinus* are readily destroyed by comparatively low temperatures. It has been emphasized by all previous workers that the toxin will not form in acid medium, but we have shown that this is not the case. Our first series of experiments show beyond all doubt that when exposed to brines containing salt in the amount of approximately 2 per cent. and lemon juice in the amount of approximately 5 per cent. a virulent toxin is developed under favorable conditions of temperature. But when the spores are exposed to the action of boiling water for one hour in acid brines of similar concentrations, as in the method of canning recommended by Cruess, or in a mixture of lemon juice of more than 2 per cent, as in our preliminary experiments, the spores are completely destroyed.

Another point of interest is that after prolonged heating, with or without the addition of lemon juice, the spores which survived were apparently damaged, since the length of time which elapsed before they germinated and grew was considerably prolonged. Whether this damage also affected the power of toxin formation has not been determined, although there is some evidence that this may be the case. In the experiments in which we tested out the cold pack method of canning fruit with or without sugar, it was found that living bacteria survived the process, although no toxin could be demonstrated in the syrup of the fruits. Subcultures of these bacteria in glucose broth produced a potent toxin, but it was not determined whether the toxin was present in as large amounts as ordinarily was formed in glucose broth. This point remained to be investigated.

The delayed germination of spores which had been exposed to prolonged heating may also be of importance in the efficiency of steriliza-

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13. We have been severely criticized for invariably inoculating the contents of the jars near the center of the jars, but we believe that we were fully justified in doing so since it is at the center that there is the greatest danger that sterilization will be incomplete. If we are to accept any method of canning as entirely efficient we must assure ourselves that sterilization is complete in all parts of the container.

tion by the fractional method, since it is possible that their delayed germination may cause them to remain in a resistant stage when the subsequent exposures to heat are made. It is possible, however, that the damaged spore is more susceptible to heat than the normal spore, and our experiments with the fractional method of sterilization would seem to bear this out, since in all instances fractional sterilization by the standard method proved to be efficient. However, we believe that for successful sterilization by the fractional method, it is necessary that the jars be sealed tightly between the exposures to heat, as otherwise undamaged anaerobic spores would fail to germinate before the final sterilization.

The experiments concerning the effect of sugar in inhibiting the development of botulinus toxin are also of interest. The efficacy of the addition of sugar as in the old fashioned process of preserving fruit, where the sugar is added in large amounts, and the fruit is "boiled down" in the syrup is undoubted, as in such a process the temperature of the boiling material rises in proportion to the concentration of sugar attained by evaporation; but in the process of canning with sugar the temperature of the material in the containers cannot rise above that of the surrounding medium no matter what concentration of sugar is present. In canning fruits with sugar, therefore, the problem resolves itself into how much the addition of sugar in itself will aid in preventing the formation of toxin if the spore of *B. botulinus* happen to be present in the raw material and survive the processing. Our experiments showed that sugar in high concentration does not, of itself, prevent the growth of *B. botulinus* or the formation of its toxin, although it does inhibit the toxin formation to a certain extent. Moreover, they show that the finished product of certain fruits canned in syrup forms a suitable medium for growth and toxin formation. We did not have an opportunity of testing the effect of heating the spores in various concentrations of sugar as we tested the various concentrations of lemon juice.

As a result of our experiments we are forced to the conclusion that various factors which have been considered efficient in canning foods are inefficient if the raw material happens to be contaminated with spores of *B. botulinus*; and certain of our experiments have revealed facts which must affect the commercial canning processes as well as home canning methods. We have not had an opportunity of investigating the commercial canner's processes, but it is well known that they are not 100 per cent. efficient in preventing spoilage. The amount of spoilage varies considerably in different packs, according to Bitting,<sup>14</sup> that type of spoilage which he describes as "swells" being

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14. Bitting, A. W.: The Canning of Foods, U. S. Dept. of Agriculture, Bureau of Chemistry, Bull. No. 151, 1912.

due to underprocessing and "more likely to be associated with rush operations."

Whether or not *B. botulinus* plays any important part in the causation of spoilage in commercially canned goods has not, in so far as we could learn, been determined. Weinzirl<sup>15</sup> in his report did not find *B. botulinus* in any of the cans which he examined, but since he discarded from his experiments all cans in which the contents were obviously unfit for food, his conclusions as to the complete absence of *B. botulinus* from commercial canned foods are scarcely justified. From his experiments he concludes that "commercial canned goods, as found in the markets, are not always sterile," and he assumes that "the living spores found in commercial canned foods are unable to grow in the food due to the absence of oxygen," but this can obviously only be interpreted to mean that in the cans which he examined he did not meet with any anaerobic spore bearing bacteria. There is nothing in his findings to indicate that had the raw material which was canned happened to be contaminated with spores of *B. botulinus*, the spores would not have survived and produced a virulent toxin.

In this respect the observations of Cheyney<sup>16</sup> are of even greater significance since his investigations were confined to commercially canned foods which were apparently fit for market. From his observation that an average of 8 per cent. of cans of food examined contained viable organisms (the percentage varied from 2 per cent. in apricots to 25 per cent. in crab), and that in a certain number of cans there was a pure culture of spore bearing bacteria, he concludes that the usual methods of processing are inefficient in that they do not result in complete sterilization. It is thus evident that in commercial canning processes as in home canning processes, the methods employed are not always efficient if the raw material happens to contain spores of *B. botulinus*.

Fortunately, the number of cases where canned foods have contained the botulinus toxin is comparatively very small; in fact, when we consider the tremendous amount of food material that is canned each year, the number of outbreaks of poisoning is exceedingly small. The greater number of outbreaks have been caused by the ingestion of home canned products, but the American medical literature contains at least two<sup>6, 17</sup> references, and we have record of a third case in which commercially canned goods are undoubtedly at fault. It is probable

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15. Weinzirl, John: The Bacteriology of Canned Foods, J. M. Research **39**:349 (Jan.) 1919.

16. Cheyney, E. W.: A Study of the Micro-Organisms Found in Merchantable Canned Foods, J. M. Research **40**:177 (July) 1919.

17. Sheppard, C.: Report of Three Cases of Fatal Ptomain Poisoning, South. Calif. Pract. **22**:370, 1907.

that the repeated examinations of the commercial products for "swells" before they ultimately reach the consumer is a safe guard which is lacking in connection with the home canned product.

But even though the number of cases of poisoning caused by the ingestion of canned goods is small, they should not be disregarded. In view of the wide distribution of *B. botulinus* throughout the country it is important that the possibility of raw material being contaminated should always be borne in mind, and investigations should be undertaken to perfect methods of canning which will be efficient in destroying this resistant organism. Until this is done it will be necessary to instruct the public of the possible danger from existing methods of canning, and to urge that all canned food which shows the slightest sign of spoilage should be discarded. If all canned food is boiled before it is eaten, any possible danger of poisoning with botulinus toxin will be removed, as the toxin is destroyed by boiling.

#### CONCLUSIONS

1. The spores of *B. botulinus* when mixed with animal or vegetable protein are much more resistant to heat than has been believed.
2. The acidification of the culture medium by the addition of 5 per cent. lemon juice does not prevent the growth of *B. botulinus* or the formation of its toxin, but the thermal death point of spores of *B. botulinus* is markedly lowered when they are heated in an acid medium of similar concentration.
3. The addition of cane sugar to beef broth in concentration up to 64 per cent. does not prevent the growth of *B. botulinus* or the formation of its toxin, although it does inhibit both to a certain extent.
4. Certain fruits which have been canned in sugar form suitable mediums for the growth of *B. botulinus* and the development of its toxin. Peaches, apricots and pears were tested.
5. Certain of the methods of canning are inefficient if the raw material happens to be contaminated with spores of *B. botulinus*. This is true of commercial canners' processes as well as of the home canning processes.

## A STUDY OF PNEUMOCOCCUS CARRIERS

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During the winter of 1917-1918, 1,311 cases of pneumonia were treated at the Base Hospital, Camp Wheeler, Ga., with 275 deaths, constituting the largest mortality of any single disease in the camp, indeed, more than 80 per cent. of all the deaths that occurred. Control of the pneumococcus infections would obviously have saved many lives to the service and avoided as well the loss of a large number of men, who were later discharged on account of physical disability, the result of complications and sequels of pneumonia.

The unenviable eminence of this camp in the matter of pneumonia is undoubtedly due to a number of coinciding predisposing factors. Perhaps most important is the character of the men here in training during the winter under discussion. Vaughan and Palmer, in the course of their exhaustive investigation of the communicable diseases occurring in the army camps in this country, have shown that susceptibility to respiratory infections varies with the character of the environment from which the soldier comes, that men from rural homes are more susceptible than those from urban homes, and other things being equal, that the men of the South are more easily infected than those of the North. Camp Wheeler presented the unlucky condition of a command largely made up of rural Southerners. Conditions of clothing and shelter incidental to the early days of the mobilization undoubtedly played a part in determining the high incidence. Many cases followed measles, and the measles and pneumonia curves follow each other very closely. The short epidemic of influenza that visited the camp early in 1918 was followed by an increased number of cases of pneumonia.

Whatever combination of predisposing causes existed, it must in the end be evident that the cause of the disease in the individual man is infection by virulent micro-organisms, in this camp predominantly the pneumococcus in one or the other of its types. In each case so infected the main facts in the process have been two, the exposure of the man to the virulent organism, and his individual susceptibility to infection. In the protection of the individual, therefore, two distinctly differing methods present themselves. One concerns itself with the building up of individual resistance, and includes all the general hygienic methods at our disposal, and specifically in many diseases at least, the use of bacterial vaccines aiming to increase the antibody content of the blood. In pneumonia, the work of Lister in South Africa, of Cecil and Austin at Camp Upton, and the more extensive work done more recently under the army pneumonia commission promise results of value from this method. On the other hand, the workers at the Rockefeller Institute have shown, by means of specific type determinations on pneumococci, that contacts of pneumonia patients often become carriers of cocci of the same type as that infecting the patient, and clinical experience has long pointed to the conclusion that the disease exists at times as an epidemic, and that contact is an important factor in its dissemination.

In confirmation of this conclusion we present the following tabulation of cases occurring in one of the battalions of the 124th Infantry. This lists the cases of pneumonia in five companies by tents, giving in each case the date of onset and the type of pneumococcus discovered. Owing to press of work and scarcity of mice, type determinations were, at that time, done only in cases seriously ill.

Analysis of this table shows that of ninety cases reported from the battalion, fifty-four, or 60 per cent., occurred in tents reporting more than one case. The largest number from one tent was eight. Whether this suggests overcrowding or is due to the infection of successive inhabitants of the tent does not appear. The ninety cases occurred in fifty-three tents. The total number of inhabited tents in the battalion is not available at this time, but a minimum number possible can be obtained by adding the numbers of the highest numbered tents of each company reporting cases. This gives 119 tents. Therefore, we may say that of this number, sixty-six tents showed no cases; thirty-two tents, one case each; seven tents, two cases each; five tents, three cases each; one tent, four cases; one tent, five cases; one tent, six cases; one tent, eight cases. As to types of pneumococci, with but few exceptions the type is seen to be the same for any one tent. This result is the more interesting when the fact is noted that the typing was done in routine, without knowledge of the tent from which the man came,

and the data assembled some months later from the records. This should eliminate any chance of prejudice in interpreting results.

From this study it would appear that contact with infected individuals or carriers plays an important rôle in the spread of pneumonia, and if, therefore, the number of carriers of virulent pneumococci in a command could be reduced, there should follow a corresponding reduc-

TABLE 1.—PNEUMONIA CASES IN FIVE COMPANIES

Outfit	Tent No.	Date of Onset	Pneumococcus Type	Outfit	Tent No.	Date of Onset	Pneumococcus Type
Co. I	3	11/28/17	Undetermined	Co. L	3	11/24/17	Undetermined
	5	12/16/17	Undetermined		8	11/16/17	Undetermined
	7	10/28/17	Undetermined		9	11/21/17	Undetermined
	7	11/ 4/17	IV		10	11/ 5/17	IV
	8	10/22/17	IV		10	12/ 1/17	Undetermined
	8	11/15/17	Undetermined		14	11/13/17	Undetermined
	8	11/28/17	Undetermined		14	11/21/17	IV
	8	11/30/17	IV		14	12/13/17	Undetermined
	8	12/ 5/17	IV		16	11/29/17	Undetermined
	8	12/10/17	IV		20	12/31/17	Undetermined
	8	12/14/17	IV		21	11/ 9/17	Undetermined
	8	12/21/17	IV		21	1/27/18	IV
	10	11/28/17	IV		21	1/31/18	1
	10	1/14/18	Undetermined		24	11/23/17	Undetermined
	11	11/23/17	Undetermined		26	11/ 3/17	IV
	11	12/19/17	Undetermined		26	11/21/17	IV
	11	12/19/17	Undetermined	Co. M	1	4/14/18	Undetermined
	11	12/27/17	Undetermined		5	1/10/18	IV
	12	12/ 1/17	II		9	11/13/17	II
	12	12/ 9/17	II		11	11/17/17	IV
	12	12/16/17	II		11	1/10/18	IV
	12	12/21/17	II		13	11/10/17	Undetermined
	12	12/30/17	II		14	12/29/17	Undetermined
	12	2/ 1/18	II		16	11/23/17	IV
	14	12/20/17	Undetermined		16	1/13/18	IV
	14	3/ 3/18	Undetermined		18	11/15/17	Undetermined
	18	10/28/17	IV		20	11/23/17	Undetermined
	18	11/ 5/17	IV		22	12/22/17	Undetermined
	18	12/ 4/17	IV		22	11/26/17	Undetermined
Co. K	3	11/ 7/17	Undetermined		32	12/27/17	Undetermined
	5	11/27/17	Undetermined		33	12/26/17	Undetermined
	9	10/29/17	Undetermined		35	1/24/18	Undetermined
	13	12/ 1/17	Undetermined	Supply Co.	4	11/28/17	Undetermined
	16	11/16/17	III		6	12/ 1/17	Undetermined
	17	12/ 5/17	II		7	12/ 3/17	Undetermined
	19	12/17/17	Undetermined		7	1/13/18	IV
	20	12/ 1/17	Undetermined		7	1/22/18	IV
	22	11/ 1/17	Undetermined		8	11/23/17	Undetermined
	28	11/23/17	II		10	11/26/17	Undetermined
	28	11/25/17	I		11	11/26/17	IV
	28	12/ 4/17	I		12	12/21/17	IV
	30	12/ 7/17	Undetermined		13	1/23/17	IV
	31	11/13/17	I		19	3/18/18	I
	31	11/26/17	I				
	31	1/18/18	I				
	31	1/18/18	I				
	31	11/13/17	IV				

tion in the number of cases of pneumonia. Our problem, therefore, divided itself into two parts, the discovery of the carrier, and the devising of means of rendering him innocuous to others. The former fell naturally to the laboratory, the latter to the medical service.

The recognized method of detecting pneumococcus carriers by means of mouse inoculations, while undoubtedly the best from the standpoint of virulence determination, would not appear to be applic-

able to large numbers of men without the services of an impracticably large force of trained workers. We have therefore used a method, for which no claim of originality is made, which we believe fulfills the requirements of this work and is exceedingly simple in application and satisfactory in its results. It is based on the fact that the pneumococcus develops a green colony when grown on a blood agar plate, which enables us to select the colonies with ease, and to apply the technic of Avery for the determination of type. Briefly it is as follows. Swabs from the nasopharynx are spread on blood agar plates, and incubated for from sixteen to twenty hours. Characteristic colonies are picked and planted in the blood broth medium of Avery. Staining is unnecessary at this stage. After incubation the growth is examined by the Gram stain, tested for bile solubility, and the cultures that qualify are further tested for type by the precipitin method. Thus each organism recorded positive has shown characteristic morphology and staining reaction, given the green colony on blood agar, and proven soluble in bile.

We have used human blood for the plates and Avery tubes and found it equally as efficacious as that of the rabbit in promoting growth and developing the color. With that exception standard methods have been employed in the preparation of media.

It was early noted that a blood broth tube inoculated from a single colony was very much slower in developing sufficiently for use than one inoculated with emulsified sputum. To determine the optimum period of incubation under these circumstances, single colonies from seventeen different strains of pneumococcus were planted in Avery's broth, and from each tube smears were made and stained at intervals up to twenty-four hours. The results are shown in the following table.

TABLE 2.—GROWTH OF PNEUMOCOCCUS IN BLOOD BROTH

Incubation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1 hour.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2 hours.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3 hours.....	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4 hours.....	0	0	0	0	0	—	—	0	0	—	0	0	0	+	0	0	0
5 hours.....	0	+	0	+	0	+	+	+	+	—	—	0	+	+	+	+	—
6 hours.....	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+
8 hours.....	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+
9 hours.....	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+
11 hours.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+
21 hours.....	—	—	—	0	—	—	—	—	0	—	—	+	+	0	+	0	0
24 hours.....	0	0	0	0	0	0	0	0	0	0	0	+	+	0	+	0	0

Under each number from one to seventeen is shown the result of the successive stains made from that tube. A zero indicates no visible growth on staining, a plus sign indicated the presence of gram-positive diplococci, while the minus sign indicates the presence of diplococci that decolorize by Gram's method. It is seen from the table that all

strains tested were autolyzed at the end of twenty-four hours, usually showing as gram-negative cocci at the examination preceding disappearance. Blood agar plates inoculated from the tubes at the end of the experiment remained sterile. Inasmuch as the bile solubility test is best applied to well preserved, actively growing cocci, the best length of incubation for this work would appear to be twelve hours.

After clearing with bile the growth is mixed with the standard dilutions of specific type sera and precipitin reactions noted. Results are uniformly clear cut and satisfactory.

In April, 1917, 700 men of the regiment mentioned above were examined by this method, one smear only being made from each man. The results are tabulated below.

TABLE 3.—CARRIERS SHOWING TYPE OF PNEUMOCOCCUS

	Number	Per Cent. of Total	Per Cent. of Carriers
Total Carriers.....	111	16.0	100.0
Carriers Type I.....	6	0.86	5.4
Carriers Type II.....	15	2.14	13.52
Carriers Type III.....	5	0.71	4.5
Carriers Type IV.....	85	12.1	76.58

This shows that 24 per cent. of the carriers and over 3 per cent. of the total number of men examined showed pneumococci of one or other of the so-called fixed types. These figures are higher than those generally accepted for the population as a whole, possibly because of the fact that the disease had been so prevalent in the organization examined in the preceding months, and many of the men were themselves recent convalescents.

The mere discovery of carriers does not promise any results of value. They must be isolated or the cocci removed from the air passages by some sort of antiseptic treatment. Isolation of 15 per cent. of a military command is obviously not a practical measure, and the problem presented to the medical service, therefore, was to find some means of sterilizing these men which should be practical, that is, easily applied by men of little training, effective and not particularly disagreeable to the subject. Further, it seemed desirable that, even if one successful method was discovered, other methods should also be tried, so that in the course of a campaign or on foreign service, if one method was not available another might be, and the work carried on in spite of limitations of material. Moreover, nothing should be done that was reasonably likely to impair the health or efficiency of the men.

By permission of the division surgeon, Lieut.-Col. Louis C. Duncan, the 111 men referred to above were admitted to the base hospital as pneumonia carriers, for the purpose of testing various methods of disinfection. To them were added several convalescent patients who still

harbored pneumococci. These men were placed in separate wards in groups of sixteen, and to each group was applied some method of treatment that seemed to promise results. This segregation was decided upon partly for the sake of control, partly for the purpose of preventing their conveying the infection to others. In order that the men might not become soft and acquire indolent habits, they were in the beginning given setting up exercises every day. Later a line officer was assigned to the convalescent wards and the men were kept fit by vigorous exercise and regular drill, so that on their return to their companies they were in better condition than when they were received.

No difficulty was experienced in persuading the men to undergo the treatment. They have all exhibited much cheerfulness. There have been no unpleasant results, except slight discomfort in one or two cases during chlorin gas treatment. These effects were of a temporary nature.

In detail the method adopted has been as follows: After a group of sixteen men had been assembled and the treatment decided on, the group was further divided into four squads of four men each. The same treatment was given to each squad, but the amount or frequency of the application varied. The treatments, as a rule, consisted of sprays or applications. The first squad was treated once daily, the second, twice, the third three times and the fourth four times, the purpose being to discover, if possible, the minimum treatment required. Cultures were made from these men at varying intervals, care being taken to obtain material in the early morning before any treatment had been received. When a man showed three negative cultures, he was regarded as clear and discharged. In some cases efforts have been made to have men report to the laboratory after some time had elapsed for the purpose of checking the ultimate result of treatment, but this has not been generally feasible. In one group no treatment was employed and cultures made to discover whether spontaneous clearing occurred.

The following is a list of measures employed:

1. Dichloramin-T dissolved in eucalyptol.
2. Dichloramin-T dissolved in chlorcosane.
3. Phenol in oil.
4. Phenol in glycerin.
5. Quinin sulphate.
6. Tincture of iodine in oil.
7. Chlorin gas.
8. Chloramin-T.
9. Eucalyptol.
10. Dobell's solution.
11. Chlorcosane.

## RECORD OF EXPERIMENTS

EXPERIMENT 1.—Dichloramin-T in eucalyptol. Spraying with pressure tank at 20 pounds; 15 seconds in each nostril and 30 seconds in throat. Begun Feb. 3, 1918, ended Feb. 17, 1918. Ten men in three groups. Cultures taken February 7, 11, and 15.

First group, four men, sprayed once daily each. All cultures negative February 7 and 11. Treatment then suspended. February 15 two men failed to return, and two were negative.

Second group, four men, sprayed twice daily each. All cultures negative February 7 and 11. Treatment then suspended. All cultures negative February 11.

Third group, two men, sprayed four times daily. All cultures negative February 7 and 11. Treatment then suspended. Cultures negative February 15.

It was concluded that Dichloramin-T is an effective agent for destroying pneumococci in the nose and throat, and that two treatments per day gave the maximum efficiency. This experiment was repeated.

EXPERIMENT 2.—Exposure to chlorin gas in the gas chamber. The concentration was 1:45,000. The duration of exposure 30 seconds. Begun Feb. 20, 1918, ended March 3, 1918. Cultures were made on the second, fourth, sixth, eighth, ninth, eleventh, thirteenth and fifteenth days.

Squad 1, exposed on first day; Squad 2, exposed on first and third days; Squad 3, exposed on first, third and fifth days; Squad 4, exposed on first, third, fifth and seventh days. The results of the experiment are shown in Table 4.

TABLE 4.—RESULTS OF EXPERIMENT 2

	Day													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
No. 1	ex	0	..	0	..	0	..	+	0	..	0	..	0	..
No. 2	ex	0	..	0	..	0	..	+	0	..	0	..	+	..
No. 3	ex	0	..	0	..	0	..	0	0	..	+	..	+	..
No. 4	ex	0	..	0	..	0	..	0	0	..	+	..	+	..
No. 5	ex	0	ex	0	..	0	..	0	0	..	+	..	+	..
No. 6	ex	+	ex	0	..	0	..	0	0	..	+	..	+	..
No. 7	ex	+	ex	0	..	0	..	+	0	..	+	..	+	..
No. 8	ex	0	ex	0	..	0	..	0	0	..	+	..	0	..
No. 9	ex	0	ex	0	ex	0	..	+	0	..	+	..	0	..
No. 10	ex	+	ex	0	ex	+	..	+	0	..	+	..	0	..
No. 11	ex	+	ex	+	ex	0	..	0	0	..	+	..	0	..
No. 12	ex	0	ex	0	ex	0	..	0	0	..	+	..	0	..
No. 13	ex	0	ex	0	ex	0	ex	+	0	..	+	..	0	..
No. 14	ex	+	ex	0	ex	0	ex	0	0	..	+	..	0	..
No. 15	ex	0	ex	0	ex	0	ex	0	0	..	+	..	+	..
No. 16	ex	+	ex	0	ex	+	ex	+	0	..	+	..	+	..
No. 17	ex	0	ex	0	ex	0	ex	+	0	..	+	..	0	..

\* "ex" indicates an exposure to chlorin gas; "0" a negative culture, and plus sign a positive culture.

This experiment is unsatisfactory. The series of negative results on the ninth day is doubtless due to technical error. Not all positive cultures were typed but in two instances types varied. Number 3 had a severe reaction from the gas and two others were made slightly uncomfortable so that we felt that the maximum dose had been employed.

On the whole, chlorin gas proved inefficient for the purpose and too dangerous for routine use.

EXPERIMENT 3.—Phenol (3 per cent.) in liquid petrolatum. Two drops were placed in each nostril and the throat swabbed at each treatment. Each man was treated twice daily. Begun March 11, 1918, ended March 27, 1918.

Squad 1, treated four days; Squad 2, treated eight days; Squad 3, treated twelve days; Squad 4, treated sixteen days. Cultures were made from all on the fifth, ninth, thirteenth and seventeenth days. All were negative with the exception of the second culture on Carrier No. 9, which yielded a pneumococcus Type I. Subsequent cultures in this case were negative.

It is therefore probable that this treatment is efficient for the purpose of destroying pneumococci in the nose and throat.

EXPERIMENT 4.—Five per cent. tincture of iodine in liquid petrolatum. Two drops in each nostril and the throat swabbed at each treatment. None of the men complained of discomfort at any time. Begun March 19, 1918, ended March 27, 1918.

Squad 1, one treatment daily for eight days; Squad 2, two treatments daily for eight days. Cultures on the fifth and ninth days. Numbers 1 and 4 were transferred to another camp at the end of eight days, and second cultures on them could not be obtained; otherwise all cultures were negative. This experiment was incomplete for reasons beyond our control, but suggests that 5 per cent. tincture of iodine in oil may be efficient.

EXPERIMENT 5.—Dichloramin-T, 2 per cent., dissolved in eucalyptol. After three days, the supply of the latter being exhausted, chlorcosane was substituted. The spray was used as in Experiment 1. Begun April 3, 1918, ended April 14, 1918.

Squad 1, treatment once daily; Squad 2, treatment twice daily; Squad 3, treatment three times daily; Squad 4, treatment four times daily. Cultures were made on the fourth, seventh, tenth and twelfth days.

Squad 1, Nos. 1 and 2, were negative three times; not cultured on the twelfth day. No. 3 was negative on the first day; positive afterward, Type IV. No. 4 was positive in all cultures except the third.

Squad 2, Nos. 5 and 8, were negative three times, not cultured the fourth time. No. 6 was negative on the first and third culture, positive on the second; not cultured the fourth time. No. 7 was positive in all cultures except the second.

Squad 3, Nos. 9 and 11, were negative except in the third culture. No. 10 was negative in the first two cultures, positive in the last two. No. 12 was negative in three cultures; not cultured the fourth time.

Squad 4, Nos. 13, 15 and 16, were negative in the first and second cultures; positive in the third and fourth cultures. No. 14 was positive in the first and third cultures, negative in the second, absent for the fourth culture.

This experiment was unsatisfactory. Eight men failed to appear for the fourth culture and could not be obtained later. The treatment was changed. On the whole, it led us to doubt the efficacy of dichloramin-T dissolved in chlorcosane.

EXPERIMENT 6.—Phenol, 3 per cent., in glycerin. Treatment given as in Experiment 3. Results are shown in Table 5. All these carriers were of Type IV and all positives later showed the same type. The results suggest that phenolized glycerin is slightly less efficacious than phenolized oil.

EXPERIMENT 7.—Quinin sulphate in 2 per cent. solution with a few drops of aromatic sulphuric acid. Applied as a spray in each nostril for fifteen seconds and in the throat thirty seconds for each treatment. Begun April 3, 1918, ended April 18, 1918.

Squad 1, treated once daily; Squad 2, treated twice daily; Squad 3, treated three times daily; Squad 4, treated four times daily. Cultures were made on the fourth, seventh, tenth, twelfth, fourteenth and sixteenth days.

Results: First culture, two positive; second culture, eight positive; third culture, four positive; fourth culture, eight positive; fifth culture, two positive; sixth culture, four positive.

Carrier 10 was reported as Type III on the second culture. All other positives were Type IV. All were originally Type IV.

We endeavored to obtain optochin for this experiment but were unable to do so. The sulphate of quinin seems of little value.

EXPERIMENT 8.—Eucalyptol from April 3, 1918, to April 8, 1918, inclusive. Dobell's solution from April 9, 1918, to April 11, 1918, inclusive. Chlorcosane from April 12, 1918, to April 17, 1918, inclusive.

No very definite results could be drawn from this experiment; the results were poor.

EXPERIMENT 9.—Chloramin-T sprayed into nostrils and throat. The treatments were given from one to four times daily. Cultures were made on the fourth, seventh, tenth, twelfth and fourteenth days. Results: First culture, one positive; second culture, five positive; third culture, seven positive; fourth culture, ten positive, two absent; fifth culture, four positive, three negative. Twelve of these men developed influenza and were transferred to the wards. A distinct tendency to somnolence was noted in the men receiving the larger number of doses daily. Chloramin-T was regarded as inefficient.

TABLE 5.—RESULTS IN EXPERIMENT 6

	Day																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
No. 1.....	1	1	1	0	1	1	0	1	1	+	1	1	0	..	..	..	..	..
No. 2.....	1	1	1	0	1	1	0	1	1	0	1	1	0	..	..	..	..	..
No. 3.....	1	1	1	0	1	1	0	1	1	0	1	1	0	..	..	..	..	..
No. 4.....	1	1	1	0	1	1	0	1	1	0	1	1	0	..	..	..	..	..
No. 5.....	2	2	2	0	2	2	+	2	2	0	2	2	+	2	2	0	2	0
No. 6.....	2	2	2	0	2	2	0	2	2	0	2	2	0	..	..	..	..	..
No. 7.....	2	2	2	+	2	2	0	2	2	0	2	2	0	..	0	..	..	0
No. 8.....	2	2	2	0	2	2	0	2	2	0	2	2	0	..	..	..	..	..
No. 9.....	3	3	3	0	3	3	0	3	3	..	3	3	..	..	..	..	..	..
No. 10.....	3	3	3	0	3	3	0	3	3	+	3	3	+	3	3	0	3	..
No. 11.....	3	3	3	+	3	3	0	3	3	0	3	3	0	3	3	+	3	0
No. 12.....	3	3	3	0	3	3	+	3	3	+	3	3	0	3	3	+	3	0
No. 13.....	4	4	4	0	4	4	+	4	4	+	4	4	0	4	4	+	4	0
No. 14.....	4	4	4	0	4	4	+	4	4	0	4	4	0	4	4	0	4	..
No. 15.....	4	4	4	0	4	4	0	4	4	0	4	4	..	..	..	..	..	..
No. 16.....	4	4	4	0	4	4	0	4	4	0	4	4	0	..	..	..	..	..

Figures indicate number of treatments daily. Plus sign indicates a positive culture, minus sign a negative culture. Blank space indicates that man was absent.

EXPERIMENT 10.—Two per cent. dichloramin-T in chlorcosane. Sixteen men in four squads. Used as spray as in former experiments.

Squad 1, one treatment daily; Squad 2, two treatments daily; Squad 3, three treatments daily; Squad 4, four treatments daily. Cultured on the fourth, sixth and eighth days: First culture, three positive, twelve negative, one absent; second culture, none positive, thirteen negative, three absent; third culture, three positive, ten negative, three absent. All the positive cultures were Type IV. This is an unsatisfactory experiment, but may be regarded as tending to the belief that the solution has some effect on the pneumococcus.

As we were particularly anxious to determine the value of dichloramin-T the preceding experiment was twice repeated under identical conditions.

EXPERIMENT 11.—Two per cent. dichloramin-T in chlorcosane. First culture, six positive, five negative, five absent; second culture, eight positive, three negative, five absent; third culture, five positive, six negative, five absent.

EXPERIMENT 12.—Two per cent. dichloramin-T in chlorcosane. First culture, five positive, eight negative, three absent; second culture, six positive, seven negative, three absent; third culture, three positive, ten negative, three absent. These experiments tend to throw doubt on the efficacy of dichloramin-T in chlorcosane. The cases not tested all remained positive.

## SUMMARY

The results of the disinfection experiments may be summarized as follows;

1. Dichloramin-T dissolved in eucalyptol gave good results. Used in solution in chlorcosane the results were far less satisfactory.

2. Chlorin gas is not efficient and caused discomfort and is possibly dangerous even in such concentration as was used.

3. Phenol as used shows good results. The solution in oil is more efficacious than that in glycerin. The use of instillations rather than sprays is perhaps preferable on account of reduced danger of ear infection.

4. Iodin in oil gave good results. It is usually available and caused no discomfort.

5. Quinin sulphate proved of no value against the pneumococcus. An accidental observation suggests that it may be valuable in another way. The experiment was under way when the spring epidemic of influenza visited the camp. The carriers of other groups were attacked by the disease in the same proportion as the men of the rest of the camp. No cases of the disease developed in the group being sprayed with the quinin. The prompt subsidence of the epidemic prevented further observations.

6. Chloramin-T is apparently of little value.

While many factors beyond our control have combined to make much of this work unsatisfactory we feel that we are justified in advancing the following conclusions and suggestions as least tentatively.

## CONCLUSIONS

1. We have at our command a technic for the detection of carriers of the pneumococcus that is simple, accurate, practical for use on large numbers of men, and open to no more objection than the methods employed so largely in the meningococcus carrier work.

2. The application of this method to 700 men showed the presence of 16 per cent. of carriers of the pneumococcus. Twenty-five per cent. of these carriers harbored organisms of the so-called fixed types. According to the figures given by Cecil and Vaughan for the pneumonia occurring in the same camp during the latter half of the same year in which these studies were made, the percentage of pneumococcus pneumonia due to organisms of the fixed types was 18.6. As this included the period of the great influenza epidemic when Type IV infections were usually prevalent, it will be seen that the proportion of fixed types among carriers and among cases is not far from the same.

3. The tent survey reported above strongly supports the idea that carriers are an important factor in the spread of pneumonia.

4. Owing to the diversity of the Type IV group as at present understood, specific vaccination against it is not practicable. In the cantonments during the war, however, this group of pneumococci has been responsible for more fatalities, and for far more disability than the organisms of the fixed types. Hence we feel justified in advocating disinfection methods directed against carriers.

5. The oily solutions of phenol and of iodine have proven most valuable in our hands for this purpose. They are usually available and easily and safely applied by untrained men.

6. We believe that the contacts of cases of pneumonia should be subjected to culture in the same way as is now done for contacts of meningitis. That when such contacts are shown to be carriers of the same type of pneumococcus as that infecting the patient, vigorous antiseptic treatment should be instituted, combined with such measure of isolation as conditions permit.

7. We wish to advance the opinion that in the presence of epidemics of pneumonia or of diseases fatally complicated thereby such as influenza or measles, it is practical to treat large numbers of men by these methods, and that such treatment should result favorably.

## ANTIPYRETICS. I. THE BENEDICT RESPIRATION CHAMBER AT THE NEW HAVEN HOSPITAL

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Comprehensive studies of antipyretic substances have not been made in recent years. While many questions bearing on relative superiority and manner of employment still require attention, the most inviting problem is, perhaps, the fundamental one of *modus operandi*. Researches in this direction should broaden our understanding of fever.

This series of papers on antipyretics will deal especially with clinical investigations of the respiratory exchange. This method of attack throws light from two important angles, the behavior of the heat balance and the nature of the materials burned.

The older antipyretics were, in their day, submitted to extensive investigation,<sup>1</sup> chiefly by the method of direct calorimetry. Although quantitative determinations of heat production and elimination were made, attention was not directed toward the respiratory quotient; nothing, therefore, is known of the relation of antipyretic action to the nature of the combustions. In this connection, the carbohydrate metabolism is of special interest in view of recent demonstrations of the influence on heat regulation which may be exerted by dextrose.<sup>2</sup>

For the purpose of studying the respiratory exchange as influenced by antipyretic substances, particularly in disease, I have installed at the New Haven Hospital a Benedict respiration chamber. This cot chamber, on account of its comparative simplicity and the comfort experienced by the subject, affords the most advantageous method of determining the respiratory exchange in the clinic. As is well known, it can be used in many pathologic cases in which mask and mouthpiece

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\* From the Department of Pharmacology, Yale University School of Medicine.

\* The expenses of this research were defrayed largely from the Francis E. Loomis Research Fund of the Yale University School of Medicine.

1. Ott, I., *Modern Antipyretics*, Easton, Pa., 1892; Fever, New York, 1914. Loewi, O.: *Ergebn. d. Physiol.* **3**:332, 1904. Textbooks of Cushny, Sollmann and Meyer-Gottlieb. The earlier calorimetric studies are unsatisfactory because sufficient emphasis has not been laid on the exclusion of muscular activity. Benedict and Homans (1911) introduced the feature of a continuous record of the state of rest or of restlessness of the subject.

2. Barbour, H. G.: *Proc. Soc. Exper. Biol. & Med.* **16**:136, 1919, and Balcar, J. O., Sansum, W. D., and Woodyatt, R. T.: *Fever and the Water Reserve of the body*, *Arch. Int. Med.* **24**:116 (July 15) 1919.

methods are impossible. The use of the chamber in conjunction with the Benedict universal respiration apparatus has been minutely described by Benedict and Tompkins,<sup>3</sup> to whose work reference should be made for the details.

The present report has a twofold purpose: First, to give a general description of the New Haven apparatus, pointing out the respects in which it differs from that described by Benedict and Tompkins; and, secondly, to record the results of certain check experiments. These results will illustrate our methods of calculation, serving especially as an index of the degree of accuracy attainable under our conditions.

#### THE NEW HAVEN HOSPITAL RESPIRATION CHAMBER

Apparatus for the entire routine, including gas analysis, is conveniently arranged in a room having the dimensions of  $19\frac{1}{3}$  by  $12\frac{1}{3}$  feet. The exposure is west, enabling the maintenance of a fairly even room temperature for the experiments, which are conducted as early in the day as feasible. The features which are in any way peculiar to

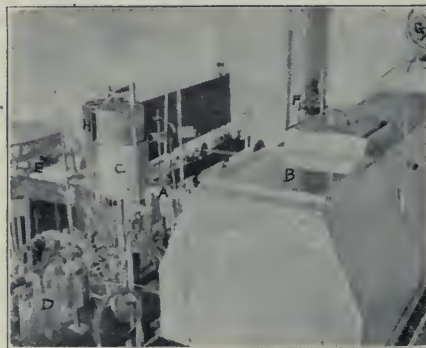


Fig. 1.—New Haven Hospital Respiration Chamber. A, position of "wet bulb" in outflow pipe. B, window. C, spirometer. D, one of the acid bottles in universal respiration apparatus. E, galvanometer. F, oxygen tank. G, fan. H, kymograph.

our apparatus relate chiefly to the size and shape of the chamber, the location of certain of its connections, the cooling system, the graphic records and other accessories.

The chamber (Fig. 1) is constructed of ordinary metal sheeting instead of copper, and presents an angular rather than a curved top. The inside dimensions are: length, 197.8 cm.; width at base, 64.5 cm.; height from constant level of water in water seal, 55.5 cm. The volume of the contained air, when no allowance is made for the spring or other

3. Benedict, F. G., and Tompkins, E. H.: Boston M. & S. J. **174**:857 (June 15) 1916; *ibid.* **174**:898 (June 22) 1916; *ibid.* **174**:939 (June 29) 1916.

contents, is approximately 637 liters. The waterseal is constructed from 3 inch gutter secured to a wooden frame, the whole base being supported by an iron pipe frame at a height of 30 inches from the floor. The  $2\frac{1}{2}$  liter spirometer which serves as the tension equalizer is connected directly with the chamber by a one-half inch pipe in its base; this pipe also receives the one-eighth inch inlet from the oxygen supply. The latter is admitted through a 1 liter Danish gas meter.<sup>4</sup> The ventilation circuit leads from the universal respiration apparatus to an opening in the base of the chamber at its foot end. It can be seen in the illustration leaving the chamber at the upper left hand corner of the head end, where the "wet" and "dry" bulb thermometers are located. The samples of chamber air which are analyzed for "residual carbon dioxid" are taken from below, through an opening in the center of the chamber base.



Fig. 2.—Chamber without cover. A, signal button. B, bulb for transmitting muscular movements to recording tambour. C, gutter serving as water seal. D, stethoscope. E, shelf for gas sampling apparatus.

The cooling system includes not only a high speed fan, but also a thin flannel blanket for summer work which closely fits the entire chamber top, and is wet thoroughly as soon as the chamber is closed at the beginning of an experiment. It is kept cool by a sprinkling device consisting of a pail of ice water which drains into a quarter inch pipe running a few inches above the chamber for its entire length. This pipe is perforated at suitable intervals and is provided with two

4. This meter has been calibrated with weighed oxygen of known purity according to the method of F. G. Benedict: *Physical Rev.* **22**:294, 1906. Our correction factor is 1.009.

cross branches at the head of the chamber. With this arrangement the average temperature is easily kept at a level no higher than from 23 to 24 C. in the hottest weather.

Besides the graphic records of muscular activity of the subject and of the time and "awake" signals, there is kept synchronously on the kymograph a tracing of the movements of the spirometer. This last serves as a check on the calculation of the admission of oxygen when necessary, and is also convenient in presenting at a glance either sudden or gradual changes in the chamber temperature.

Other accessories are the 2-inch Bowles' stethoscope, kept secured to the subject's chest, by which the pulse rate and the electric thermocouples for the rectal temperature are followed. The thermocouples consist of copper—constantan (No. 25 gage) junctions; one of which is kept at a distance of about 10 cm. within the rectum; the other in a Dewar flask outside the chamber. A Leeds and Northrup portable mirror galvanometer (No. 2,400 A) is used. As now installed, 8.8 units on the scale correspond to 1 C. At the beginning and close of every experiment with a subject the galvanometer readings are checked by a mercurial thermometer.

#### CHECK EXPERIMENTS

Alcohol<sup>5</sup> check experiments are made at frequent intervals to demonstrate that the chamber remains air-tight. The results of two such experiments are presented in Tables 1 and 2.

TABLE 1.—ALCOHOL CHECK EXPERIMENT MADE MAY 1, 1919, TO DEMONSTRATE THAT THE CHAMBER REMAINS AIRTIGHT

Period	Duration in Minutes	Residual Carbon Dioxid	Liters Carbon Dioxid			Carbon Dioxid, C.c. per Minute	Liters Oxygen			Oxygen, C.c. per Minute	Respiratory Quotient
			Difference	Absorbed by Soda Lime	Produced		Oxygen plus Nitrogen	Difference	Admitted	Consumed	
B	..	2.49	.....	.....	.....	.....	582.15				
P	47	1.77	-0.72	8.40	7.68	163.42	585.29	+3.14	15.20	12.06	0.64
I	30	2.02	+0.25	4.84	5.09	169.67	584.89	-0.40	7.13	7.53	0.68
II	32	1.77	-0.25	5.10	4.85	151.56	585.69	+0.80	8.08	7.28	0.67
III	37	1.78	+0.01	5.83	5.84	157.84	585.37	-0.32	8.81	9.13	0.64
IV	29	1.77	-0.01	4.50	4.49	154.83	585.09	-0.28	6.46	6.74	0.67
V	30	1.71	-0.06	4.67	4.61	153.67	585.95	+0.86	7.53	6.67	0.69
VI	31	1.54	-0.17	4.69	4.52	145.16	585.32	-0.63	6.14	6.77	0.98
VII	35	1.65	+0.11	5.09	5.20	148.57	583.78	-1.54	6.47	8.01	0.65
VIII	28	1.54	-0.11	4.04	3.93	140.36	584.17	+0.89	6.19	5.80	0.68
Total	299	....	.....	....	46.21	154.55*	.....	.....	....	69.99	0.66*

\* Average.

5. The theoretical respiratory quotient for alcohol is 0.667. The slightest leak in the closed system causes the carbon dioxid and oxygen determinations to vary from the true figures in opposite directions, thus making an appreciable error in the respiratory quotient.

In addition, the respiratory quotients for periods of ninety-four minutes or less, given in Table 3, have been obtained.

These alcohol checks show that the theoretical respiratory quotient for alcohol is attainable when the apparatus is operated continuously for a number of half-hour periods. In the two cases detailed in Tables 1 and 2, the preliminary periods (P) afforded satisfactory respiratory quotients; but since it may require some time for the temperature of the chamber to become stabilized, we never rely on the oxygen figure for the preliminary period. After the ventilation system has been running for thirty minutes, however, satisfactory respiratory quotients (maximum variation  $\pm 0.03$  can be obtained for each individual half-hour period.

TABLE 2.—ALCOHOL CHECK EXPERIMENT MADE JUNE 30, 1919, TO DEMONSTRATE THAT THE CHAMBER REMAINS AIRTIGHT

Period	Duration in Minutes	Carbon Dioxid, C.c. per Minute	Oxygen, C.c. per Minute	Respiratory Quotient
10:16½ P	33½	259.70	372.54	0.697
10:49½ I	33½	256.24	399.10	0.642
11:24½ II	34½	247.22	376.97	0.662
12:00½ III	36½	233.93	335.72	0.697
I-III	104½	245.46*	368.63*	0.666*

\* Average.

TABLE 3.—RESPIRATORY QUOTIENTS

Date	Duration of Preliminary Period, Minutes	Duration of Calculated Period, Minutes	Respiratory Quotient
Feb. 3, 1919.....	21	62	0.670
May 7, 1919.....	30	90	0.665
June 9, 1919.....	36	94	0.665
June 17, 1919.....	30	92	0.659

TABLE 4.—RESULTS OF OBSERVATIONS MADE ON A NORMAL INDIVIDUAL (W. J. C.); WEIGHT, 81.1 KILOGRAMS; SURFACE AREA, 2.02 SQUARE METERS (EXPERIMENT OF APRIL 1, 1919)

Time	Duration	Liters		Respiratory Quotient	Per Minute				Per Square Meter per Hour	
		CO <sub>2</sub> Produced	O <sub>2</sub> Consumed		CO <sub>2</sub> C.c.	O <sub>2</sub> C.c.	Calories Produced	Calories Eliminated	Calories Produced	Calories Eliminated
2:55 (P)										
3:25 (I)	30	6.86	8.08	0.85	229	269	1.30	....	38.6	
3:55 (II)	30	7.10	8.25	0.86	237	275	1.34	....	39.8	
4:28 (III)	33	7.67	8.84	0.88	232	265	1.32	....	39.2	
Total	93	21.63	25.17	0.86*	233*	271*	1.32*	1.22*	39.2*	35.9*

\* Average for three periods.

*Calculation of an Experiment with a Human Subject.*—The data presented in Table 4 will serve to illustrate the use of the apparatus with a normal human subject.

It will be seen that the half-hour figures for the respiratory quotient stand in excellent agreement. Since the half-hour oxygen data were, especially in the earlier months of our experience, usually more at variance than in this experiment, we have been accustomed, up to the present time, to calculate the heat production in calories from the half-hour carbon dioxid determinations. The calory factor employed is the one which corresponds to the average respiratory quotient for the day, i. e., ninety or more minutes. In the experiment outlined in Table 4, for example, the average respiratory quotient for the three periods was 0.86, for which the calory factor is 5.669. Multiplying each carbon dioxid determination by this factor one obtains, respectively, 1.30, 1.34 and 1.32 calories per minute. For a surface area of 2.02 square meters (Dubois linear formula) this gives, respectively, 38.6, 39.8 and 39.2 calories per square meter per hour, or an average of 39.2 calories for the whole experiment.

When the method of indirect calorimetry is employed, heat elimination can be determined only by following the average body temperature. The rectal temperature, although it gives under ordinary conditions an absolute value which is something like 0.5 C. too high,<sup>6</sup> affords a fair criterion when employed only for differential purposes, i. e., to determine the *changes* in average body temperature. In the experiment of April 1, 1919, the rectal temperature curve showed a net change of +0.14 degrees during the ninety-three minutes. The subject weighing 81.1 kilograms and having a thermal equivalent of 67.3 ( $81.1 \times 0.83$ ), therefore stored 9.42 ( $67.3 \times 0.14$ ) calories during this time. This gives an average accumulation of 0.10 calories per minute, which, subtracted from a heat production of 1.32 calories, gives a total elimination of 1.22 calories per minute, or 35.9 calories per square meter per hour.

#### CONCLUSIONS

The Benedict respiration chamber appears admirably adapted to clinical studies of the respiratory exchange. After the ventilation circuit has been run for a preliminary period of thirty minutes, half-hour periods are of sufficient length for following the heat balance. The respiratory quotient can, within ninety minutes, be determined with a high degree of accuracy. For the individual half-hour periods, the variation in the respiratory quotient need not be over  $\pm 0.03$ .

The procedure is certainly well tolerated in every way by many patients on whom investigations by mask or mouthpiece methods would be impracticable.

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6. Barr, D. P., and DuBois, E. F.: Clinical Calorimetry, Arch. Int. Med. 21:627 (May) 1918.

## ANTIPYRETICS. II. ACETYLSALICYLIC ACID AND HEAT REGULATION IN NORMAL INDIVIDUALS \*

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Acetyl salicylic acid (aspirin), introduced into therapeutics by Dreser,<sup>1</sup> is today the most widely used of antipyretic drugs. Its action on the heat regulating mechanism has, however, been subjected but little to careful investigation. That other salicylates possess antipyretic and analgesic properties of a feebler order than those of acetylsalicylic acid was emphasized by the work of Bondi and Katz,<sup>2</sup> who associated the difference with the fact that the acetyl ester appears to be absorbed and distributed largely intact, salicylate being but slowly split off in the intestine.

The effects of this substance on the heat regulation of normal and of febrile human subjects, respectively, will be dealt with here and in the third paper of the series. Essentially, they are studies of the respiratory exchange in correlation with the body temperature.

### LITERATURE OF SALICYLATES IN RELATION TO HEAT REGULATION

Buss<sup>3</sup> investigated the effects of sodium salicylate on the carbon dioxide production both of normal subjects and of patients with typhoid, tuberculosis and diphtheria. This was done with the Liebermeister apparatus, which from the present day standpoint can scarcely be regarded as adapted to the making of accurate determinations. Furthermore, the preparation employed by this author appears to have contained a high percentage of sodium cresotinate, a substance which appears to possess similar properties.

Buss found that sodium salicylate (in doses of from 6 to 8 gm.) produced in his fever patients no reduction of the carbon dioxide output in spite of reductions in temperature of several degrees centigrade. There was often in fact an increase in the carbon dioxide after an hour or more had elapsed. He states that similar doses in normal individuals give no diminution in the carbon dioxide production, but it does not appear whether or not these cases may have exhibited an increased output.

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\* From the Department of Pharmacology, Yale University School of Medicine.

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1. Dreser, H.: *Pflüger's Arch.* **76**:306, 1899.

2. Bondi, S. & Katz, H.: *Ztschr. f. klin. Med.* **72**:177, 1911.

3. Buss, C. E.: "Ueber Wesen und Behandlung des Fiebers," Stuttgart, 1878.

Livon<sup>4</sup> found with one exception a decided increase in the carbon dioxide production in experiments on guinea-pigs, turtles and frogs with sodium salicylate.

Wood and Reichert<sup>5</sup> gave from 1 to 5 gm. doses of sodium salicylate to normal dogs. A 43.3 per cent. increase in heat dissipation was calculated by means of a water calorimeter. This was associated with an increase of 39.6 per cent. in the heat production.

Stuehlinger<sup>6</sup> studied the action of sodium salicylate on normal guinea-pigs in a Rubner calorimeter. The effects on body temperature were variable. Five of the six experiments showed changes in the heat production varying from a 4 per cent. loss to a 10 per cent. gain. The other case showed an 82 per cent. gain. The heat dissipation was in every case increased, the change varying from 2 to 4 per cent. above normal, except in one case showing a 59 per cent. increase.

Apparently the only modern studies of sodium salicylate on the respiratory exchange are those of Denis and Means,<sup>7</sup> who studied three men from the surgical wards of the Massachusetts General Hospital. Benedict's universal respiration apparatus with spirometer and mouth piece were used. Observations were made with the subjects in a fasting condition and at complete rest. Each day's experiment consisted of three ten minute periods. Subject 1, aged 28 years, after receiving 15.45 gm. sodium salicylate over a period of three days, exhibited a rise of 15 per cent. above the basal metabolism (mild salicylism noted). Subject 2, aged 41 years, was described as mildly septic and apparently had a high basal metabolism at the beginning. There was no change noted after 23.45 gm. sodium salicylate had been administered over a period of four days. Subject 3, aged 64 years, took 19.2 gm. sodium salicylate over a period of three days without altering his basal metabolism. The respiratory quotations were not altered by the drug.

To summarize the results of these investigations on sodium salicylate, it may be said that after rather large doses, evidence of an increase in the heat production has been found frequently but not constantly in normal animals and man. No conclusion can be reached as to the effects of sodium salicylate on the total metabolism of the febrile organism.

The effects of acetylsalicylic acid on the energy exchange have apparently never been submitted to serious investigation. A careful search for literature bearing on this point has brought to light only the three rabbit experiments of Singer.<sup>8</sup> This author determined the oxygen consumption in normal animals, employing a Regnault-Reiset apparatus. Two rabbits received each 0.3 gm. acetyl salicylic acid *per os* and exhibited decreases in the oxygen consumption of 17 and 14 per cent. respectively; a "toxic" dose, 0.9 gm. in the third animal, was followed by a 9 per cent. increase.

#### PRESENT WORK

*Subjects.*—Five normal individuals served as subjects, including three medical students besides the authors. Descriptive data are given in Table 1.

*Apparatus.*—The Benedict respiration chamber and other apparatus employed have been described in the first paper of this series.<sup>9</sup>

4. Livon, Ch.: Compt. rend. Acad. d. sc. **90**:321, 1880.

5. Wood and Reichert: J. Physiol. **3**:321, 1882.

6. Stuehlinger: Arch. f. exper. Path. u. Pharmacol. **43**:166, 1900.

7. Denis, W., and Means, J. H.: J. Pharmacol. & Exper. Therap. **9**:273, 1916.

8. Singer, H.: Pflüger's Arch. **84**:527, 1901.

9. Barbour, H. G.: Arch. Int. Med., this issue, p. 611.

*Procedure.*—Owing to other engagements of the subjects, it was not feasible to conduct this series of experiments in the morning. A very light breakfast was therefore allowed at least six hours previous to the beginning of the experimental period. The breakfast did not include meat or eggs, and was always identical in the case of two or more experiments on the same individual.

TABLE 1.—DATA ON EXPERIMENT SUBJECTS

Subject	Age, Years	Weight, Kg.	Surface Area, Square Meters (Dubois' Linear Formula)	Acetyl- salicylic Acid, Gm.
H. G. B. ....	33	64.8	1.76	1.0
M. M. D. ....	27	59.8	1.69	1.0
W. Y. S. ....	23	71.1	1.84	1.0
W. J. C. ....	31	81.1	2.02	1.25
H. J. S. ....	33	68.9	1.81	1.0

The subject lay down on the cot fifteen minutes before the cover was put in place. During this period the stethoscope and rectal thermocouple were adjusted and preliminary readings taken of pulse and body temperature. The latter reading at the beginning and end of each day's work was controlled by a mercurial thermometer.

One or 1.25 gm. acetylsalicylic acid were given by mouth with 250 c.c. water. The drug was given sometimes before closure of the chamber, but more often toward the end of the "preliminary period." In the control experiments the same amount of water was given without the drug. In two of the experiments reported here, control periods were run on the same day and previous to the drug experiment. This procedure was ultimately abandoned, being too tedious for the subject.

As soon as the cover was lowered the air mixer within the chamber was started; at the end of fifteen minutes the ventilation circuit was turned on, enough carbon dioxid having accumulated by this time to furnish a fairly constant residual level. A preliminary period of from 30 to 45 minutes followed before the beginning of the experimental period proper, from which the results are reported. The latter period lasted from one and one half to two hours. This was divided approximately into half-hour periods, the change between periods always being deferred when necessary to a moment when the chamber temperature was exhibiting little or no fluctuation. All of the determinations of chamber temperature, barometric pressure, body temperature, pulse, etc., were made as nearly as possible at the moment when one period closed and the next began. The samples of chamber air for the residual carbon dioxid were, of course, taken at this time also.

The results were all calculated as described in Paper I.

## RESULTS

The results of six control experiments and five experiments with acetylsalicylic acid are tabulated in Table 2. Attention may be called to the following points:

*Carbon Dioxid Production.*—It will be seen that this was definitely higher after the drug had been taken in the case of four out of the five individuals, the first exhibiting practically no difference.

*Oxygen Consumption.*—The oxygen consumption changes are similar, showing that therapeutic doses of acetyl salicylic acid in normal individuals exhibit in the majority of cases a mild stimulation of the total metabolism.

*Respiratory Quotient.*—Since the respiratory quotients given represent a period of one and one-half or more hours' continuous experimentation, they may be regarded as sufficiently accurate for the calculation of the heat production in calories. There is probably no change in the nature of the materials burned, for the results as a whole indicate that the drug, in this dosage, does not alter the respiratory quotient of normal persons.

CAL. per sq. m per hr

45

40

35

↑ A-S.A 1 Gm

0 hr.

1 hr.

2 hrs

Heat production in calories per square meter per hour. Broken line: Average normal level for the five subjects. Unbroken line: Determinations following ingestion of acetylsalicylic acid, given at the zero hour. Date of each experiment (Table 2) noted at its initial point.

*Heat Production.*—When expressed as calories per square meter per hour (by calculation from the respiratory quotient for the day), it will be seen that the average increase in heat production for the entire series of drug experiments amounted to 6.1 per cent. above normal. The change is best shown in the diagram, where each experiment is plotted in the proper time relation to the arrow representing drug administration. The broken line indicates the average level of heat production for the same individuals without the drug.

During absorption of the drug the figures are grouped around the normal level. The maximal effect appears during the fourth half hour after administration, at which time the heat production is above normal

TABLE 2.—RESULTS OF ADMINISTRATION OF ACETYLSALICYLIC ACID TO NORMAL SUBJECTS

Subject	Date	C.c. per Minute				Respira- tory Quo- tient	Per Square Meter per Hour				Body temperature		Pulse Rate	
		Carbon Dioxid Production		Oxygen Absorption			Calories Produced		Calories Eliminated					
		Control	Acetyl- salicylic Acid	Control	Acetyl- salicylic Acid		Control	Acetyl- salicylic Acid	Control	Acetyl- salicylic Acid	Change, C.	Initial, C.	Change per Min.	Initial per Min.
H. G. B.	2-27 4-9	205 ...	203 243	246 ...	...	0.84 0.83	40.4 37.7	...	42.3 36.7	...	-0.13 -0.08	37.46 36.98	-8 +2	68 64
M. M. D.	2-20	179	183	...	226	0.81	37.7	38.7	39.0	39.0	+0.02, -0.02	36.65	+4, -4	68
W. Y. S.	1-23	203	237	...	...	0.89	36.5	42.6	42.7	38.0	-0.20, +0.22	36.67		
W. J. C.	4-1	...	233	...	271	0.86	...	39.2	...	35.9	+0.15	36.60		
	4-3	218	...	247	...	0.88	36.1	...	37.2	...	-0.05	36.59	-8	72
H. J. S.	3-24 4-15	213 207	213 ...	243 238	...	0.87 0.87	...	40.6 ...	...	41.9 ...	-0.13 -0.04	37.04 36.83	-9 0	63 54
Average Change	.... ....	.... ....	.... ....	.... ....	.... ....	.... ....	37.82 ....	40.28 +6.1%	39.62 ....	39.34 -0.7%				

in all seven cases. (Two cases plotted are not included in Table 2 because of the factor of sleep.)

*Heat Elimination.*—As explained in the first paper of this series, heat elimination was calculated on the assumption that changes in the rectal temperature run parallel to changes in average body temperature. On this basis there was found in the entire series no significant difference in the heat elimination between normal and drug experiments; in the latter case it was 0.7 per cent. less than in the former.

*Body Temperature.*—The failure of the heat elimination to increase proportionately to heat production is associated with a relatively slight increase in the body temperature. The table shows that there was a tendency for the body temperature to fall somewhat (average,  $-0.08$  C.) during the experimental period when no drug was given. The acetylsalicylic acid, by increasing the heat production, overcompensated for this fall, but never raised the body temperature more than  $0.22$  C. above the starting point, the average increase being  $+0.03$  C. The initial body temperature for each experiment is presented in the second temperature column.

*Pulse Rate.*—The last two columns show that acetylsalicylic acid exerts no constant effects on the slow pulse of a normal individual at complete muscular rest in a nearly fasting condition.

#### SLEEP EXPERIMENTS

In two additional experiments the subject was allowed to sleep as long as possible; in each case this amounted to about one hour. The details are as follows:

EXPERIMENT OF MARCH 10, 1919.—H. G. B. took 1 gm. acetylsalicylic acid at 2:10 p. m.—in this case near close of preliminary period. He slept from 3 to 4 p. m. During the period from 2:25 to 4:25 p. m., the average carbon dioxid production was 197 c.c. per minute, the average oxygen consumption 222 c.c. per minute, giving a respiratory quotient of 0.89. Heat production and elimination were respectively 38.2 and 35.7 calories per square meter per hour. Temperature at 2:30 p. m. was  $37.2$  C.; at 3:25 p. m.,  $37.1$  C.; at 4:25 p. m.,  $37.35$  C.

*Calory production by half-hour periods (Fig. 1):* 37.2; 35.8; 41.2; 38.4.

EXPERIMENT OF MARCH 13, 1919.—M. M. D. took 1 gm. acetylsalicylic acid at 2:55 p. m., during the end of the first period. He slept from 3:28 to 4:18 p. m. From 2:55 to 5:04 p. m. the average carbon dioxid production was 179 c.c. per minute, average oxygen consumption 216 c.c. Respiratory quotient, 0.83. Average heat production and elimination, respectively, 38.3 calories and 41.7 calories per square meter per hour. The body temperature at 2:55 p. m. was  $36.75$  C.; at 5:05 p. m. it was  $36.5$  C.

*Calory production by half-hour periods (Fig. 1):* 36.9; 36.2; 41.3.

Notwithstanding the practically perfect freedom from activity achieved, it will be seen that in both experiments a much higher level of heat production was attained in the second than in the first hour

after taking the drug. The best evidence of its stimulating effect on the metabolism is thus afforded.

*Does Sleep Favor the Exhibition of Antipyretic Action?*—One purpose of these two experiments was to determine whether a condition of narcosis would have any influence in bringing to light the antipyretic action of acetylsalicylic acid which is otherwise not exhibited in normal individuals. Had an affirmative result been reached, an analogy might have been drawn between sleep and fever.

Since no significant temperature depression could be elicited under these conditions, we concluded that sleep does not favor the exhibition of antipyretic action by the drug.<sup>10</sup> Sensitivity to antipyretics probably depends therefore on something different from central depression. This militates against the theory that antipyretic action is a manifestation of central stimulation. (See following paper.)

#### CONCLUSIONS

1. Normal individuals usually respond to acetylsalicylic acid (1 gm. per os) by an increase in the carbon dioxid output and heat production. The maximum effect is reached during the fourth half hour after administration.

2. The average heat production of five subjects was 40.3 calories per square meter per hour after taking the drug, as against the basal average, for these persons, of 37.8 calories; an increase of 6.1 per cent. was thus indicated.

3. In spite of the increased metabolism, heat dissipation was not significantly altered.

4. During the control experiments the average change in body temperature was  $-0.08^{\circ}\text{C.}$ ; after the drug it was  $+0.03^{\circ}\text{C.}$

5. The respiratory quotient does not appear to be altered by the drug in normal individuals. The same is true of the pulse rate.

6. Sleep does not appear to favor the exhibition of antipyretic action by acetylsalicylic acid.

The authors take pleasure in acknowledging with thanks the very helpful coöperation of Messrs. W. J. Craig, W. Y. Sayad and H. J. Stander, who acted as subjects in some of the experiments.

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10. The state of sleep has, if anything, tended to bring out the stimulating effect of the drug on heat production. (See third period of each experiment.) Cf. effect of antipyrin and of sodium salicylate on decerebrate animals as described by Barbour and Deming, *J. Pharmacol. & Exper. Therap.* **5**:149, 1913, and by Isenschmid, *Arch. exper. Path. u. Pharmacol.* **75**:10, 1913.

## ANTIPYRETICS. III. ACETYLSALICYLIC ACID AND HEAT REGULATION IN FEVER CASES \*

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NEW HAVEN, CONN.

In the foregoing paper<sup>1</sup> it has been shown that acetylsalicylic acid, in 1 gm. doses, has but a slight effect on the heat balance of normal individuals. An average increase of 6.1 per cent. above the normal heat production was obtained in five cases, the maximum effect occurring during the fourth half hour after giving the drug by mouth. A very slight tendency to raise the body temperature was observed. In this paper will be reported the effects of acetylsalicylic acid given in the same amounts in fever cases. As will be seen from the data, during febrile and afebrile phases, as well as in the first stages of convalescence, similar phenomena have been manifested.

In determining the means by which a substance exerts its antipyretic action, it is necessary to know how the energy exchange is affected. Is the reduction in temperature due to an increase in heat elimination or to a decrease in heat production, or are both of these factors concerned in its action?

### LITERATURE

As will be seen from the preceding paper, no calorimetric work has been done on acetylsalicylic acid in fever. This is somewhat surprising in view of its alleged superiority<sup>2</sup> as an antipyretic to other salicylates. Sodium salicylate was investigated by Buss,<sup>3</sup> using primitive methods, in cases of typhoid, tuberculosis and diphtheria. His conclusion was that this substance produces no reduction in the carbon dioxid output in fever. At the present time it is generally assumed that salicylates exert antipyretic action merely by increasing the heat elimination, as do the members of the antipyrin group.

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\* From the Department of Pharmacology, Yale University, School of Medicine.

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1. Barbour, H. G., and Devenis, M. M.: *Arch. Int. Med.*, this issue, p. 617.

2. Bondi, S. & Katz, H., *Ztschr. f. klin. Med.* **72**:177, 1911.

3. Buss, C. E.: "Ueber Wesen und Behandlung des Fiebers," Stuttgart. 1878, pp. 67-76.

## METHOD

The present work has been done with the Benedict respiration chamber at the New Haven Hospital described in the first paper<sup>4</sup> of this series. The data given in Table 1 relate to the five subjects investigated:

TABLE 1.—DATA ON SUBJECTS OF EXPERIMENT

Subject	Age, Years	Weight, Kg.	Surface Area, Square Meters (Dubois' Linear Formula)	Acetylsalicylic Acid, Gm.	Diagnosis	Illness Began
J. D.	25	52.21	1.50	1.0	Tuberculosis (cold abscess)	11/24/18
G. G.	30	49.94	1.54	1.0	Tuberculosis (kidney)	3/21/19
G. M.	14	26.55	1.21	0.75	Osteomyelitis (convalescent)	12/ 6/18
T. W.	47	46.21	1.56	1.0	Pneumococcus empyema (convalescent)	1/16/19
S. L.*	28	55.21	1.63†	1.0	Acute pulmonary tuberculosis	7/12/19

\* S. L. received no breakfast.

† Dubois' height-weight formula.

*Procedure.*—The same procedure was employed as described in the second paper<sup>5</sup> with the exception that the experiments were performed in the morning, preceded by three hours by the small breakfast suggested by Soderstrom, Barr and DuBois.<sup>6</sup>

The results divide themselves into a larger group, relating to the effects of acetylsalicylic acid during the exhibition of its antipyretic action and a group of two experiments which illustrate the conditions prevailing during the reaction toward the initial temperature.

The results in the first group, with one exception, appear in Table 2, which includes a control experiment on each of four individuals and six drug experiments on the same group.

*Temperature Changes.*—The changes in body temperature noted in the table occurred in each case during the exact period for which the metabolism results are reported. It will be seen that on the days on which no drug was given there was a rise in temperature in three out of four cases, the fourth case exhibiting a slight fall. After acetylsalicylic acid, however, a marked temperature fall was observed in every case. This averaged more than 0.8 C. in ninety minutes for the series.

It will be noted that this fall took place in spite of the fact that the initial temperatures were usually but slightly elevated and in some cases were normal. It should therefore be said of antipyretic drugs not that they reduce only an elevated temperature, but that they *reduce*

4. Barbour, H. G.: Arch. Int. Med., this issue, p. 611.

5. Barbour and Devenis, Arch. Int. Med., loc. cit.

6. Soderstrom, G. F., Barr, D. P. and Dubois, E. F.: Arch. Int. Med. **21**: 613 (May) 1918.

the temperature in fever cases, afebrile stages and a part of the convalescence period being included.

*Carbon Dioxid Production.*—When one compares the carbon dioxid production after acetylsalicylic acid with that under the control conditions, the increase exhibited in normal individuals is seen but twice in six cases. The other experiments show a slightly decreased carbon dioxid output, but no more than can be accounted for by the fall in body temperature.

*Oxygen Consumption.*—The oxygen consumption was increased by the drug in only one case, affording evidence that these doses of acetylsalicylic acid cause, if anything, a diminution in the energy exchange of febrile individuals.

*Respiratory Quotient.*—It will require a greater number of respiratory quotients than can be reported at present to determine definitely whether acetylsalicylic acid alters the nature of the combustions in febrile cases. Taking the evidence which Table 3 furnishes, together with one case not included therein (because of an unsuccessful control experiment which it was not feasible to repeat), we have an average respiratory quotient of 0.83 for five control experiments, which is increased to an average of 0.87 for seven drug experiments. As this increase appears in four out of five subjects, the tentative suggestion may be allowed that acetylsalicylic acid increases the respiratory quotient in febrile subjects. This increase would indicate that in the metabolic processes of such individuals the drug arouses a more active participation by the carbohydrates. This question is now being investigated in this laboratory from a number of viewpoints.<sup>7</sup>

*Heat Production.*—When the carbon dioxid production is converted to calories per square meter per hour, the average change in metabolism caused by the drug in this series may be expressed as — 3.5 per cent.

*Heat Elimination.*—Taking into account the changes in body temperature, the number of calories eliminated have been calculated as explained in Paper I<sup>8</sup> for both of our series of experiments. It will be seen that each individual lost much more heat after the drug than without it. The average heat elimination in the control experiments amounted to 37.7 calories per square meter per hour, while with acetylsalicylic acid, 52.1 calories per square meter per hour were lost by the same subjects, showing an increase of 38.2 per cent. Contrasting this figure with the insignificant change in the heat production, the fact becomes established that this drug exerts its antipyretic action almost entirely by means of an increased dissipation of heat. This

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7. Barbour, H. G.: "The Antipyretic Action of Dextrose," *Proc. Soc. Exper. Biol. & Med.* **16**:136, 1919.

8. Barbour, H. G.: *Arch. Int. Med.*, this issue, p. 611.

has, of course, often been surmised from observation of the marked diaphoresis and increase in surface temperature.

*Pulse.*—Some diminution in pulse rate was observed in nearly all the experiments. This amounted to an average of one beat per minute for every half hour, in the controls; after taking the drug, however, the difference amounted to  $3\frac{1}{3}$  beats per minute for each half hour. In one case a temporary disturbance in rhythm occurred and in another (G. M.) a reduction of the rate by nearly one half occurred for a short time, very suggestive of temporary heart block. Certainly one cannot overlook the possibilities of cardiac disturbances resulting from the use of large doses of this drug.

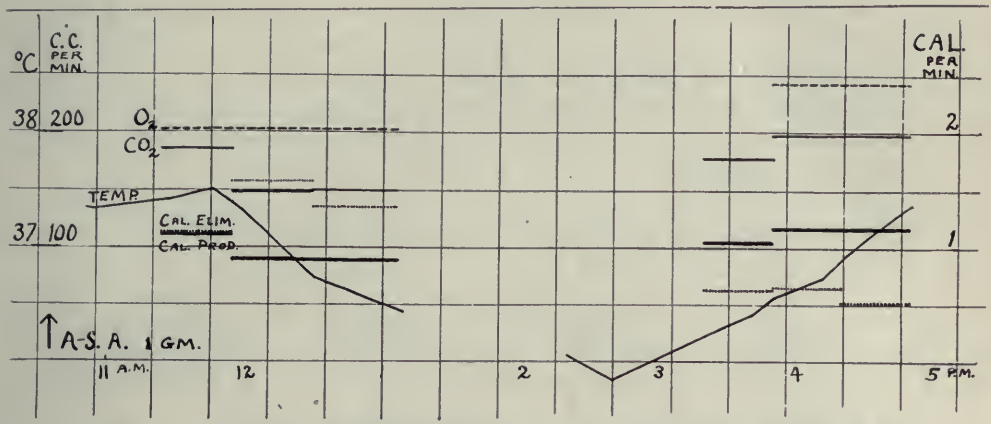


Fig. 1.—Effects of acetylsalicylic acid on J. D. (tuberculous abscess). First half, antipyretic phase; second half, return to initial temperature (another day with essentially the same morning temperature curve).

--- oxygen, c.c. per minute  
 — carbon dioxide, c.c. per minute  
 / \ body temperature  
 — calories produced per minute  
 .... calories eliminated per minute  
 Abscissae: hours  
 Drug administered at arrow both days.

Supplementary to the above results may be mentioned the acetylsalicylic acid experiment on S. L. (July 22, 1919), for which no satisfactory control was obtained. This subject had taken no breakfast at all. The carbon dioxide production and oxygen consumption per minute were respectively 185 and 231 c.c., giving a respiratory quotient of 0.80 and 41.2 (carbon dioxide) calories produced per square meter per hour.

The heat elimination was 45.2 calories per square meter per hour. This figure is sufficiently above all of our control determinations in other subjects to lend support to the conclusion that the drug exerts its antipyretic action by stimulating the heat dissipating process.

The temperature change in this experiment was  $-0.28^{\circ}\text{C}$ ., the initial temperature of the subject being  $37.23^{\circ}\text{C}$ . The pulse change was  $-2$  beats per minute per half hour.

In Figure 1, is presented graphically the progress by half hour periods of a typical acetylsalicylic acid experiment. The oxygen consumption given (indicated by the dash line), is the average for the entire experiment. The chief diminution in the carbon dioxid output and heat production is seen to take place during the periods of greatest temperature decline. The change in heat production appears slight when compared with the great increase in heat elimination seen during the second period. The maximum effects of the drug appear during the second hour after administration.

*Return to Initial Temperature.*—This is presented in the last half of Figure 1, taken from the same subject as the first half, but on a different day, the proper time relation to the injection of the drug being maintained. The rectal temperature in this case was followed during the morning and agreed essentially with that shown in the first part of the diagram.

TABLE 2.—CARBON DIOXID PRODUCTION DURING RETURN TO INITIAL TEMPERATURE AFTER TAKING ACETYLSALICYLIC ACID

Time	Acetyl-salicylic Acid, Gm.	Rectal Temperature, $^{\circ}\text{C}$ .	Carbon Dioxid Production (C.c. per Minute During Foregoing Period)
9:00 a. m.	...	37.4	
9:15 a. m.	1.0	37.4	
10:00 a. m.	...	37.2	
11:00 a. m.	...	37.2	
12:55 p. m.	...	37.03	
1:55 p. m.	...	36.70	
2:33 p. m.	...	36.91	189.71
3:00 p. m.	...	37.01	193.23
3:30 p. m.	...	37.28	181.48
Average.....			187.78

It is evident that the return to the initial temperature after acetylsalicylic acid is not associated, as the ascending curve of fever often is, with a marked increase in the heat production; the change is even less than that occurring with the antipyretic effect. Diminution in elimination of heat is the striking feature of the return to initial temperature; this amounted to less than 50 per cent. of the normal figure in the last half hour period shown.

This reaction after antipyretic action was associated with absence of sweating but there was no shivering or sensation of chilliness.

Similar results were noted in an experiment with the subject, G. G. (April 12, 1919). The carbon dioxid production was determined for ninety-nine minutes, beginning with the turning point of the temperature curve. The data shown in Table 2 were obtained.

It will be seen that during the period of reaction from the antipyretic effect, this subject's average carbon dioxid production was slightly lower than on March 5, when no drug was given. Assuming a respiratory quotient of 0.91 (average of this subject's quotients in Table 3) the heat production in this experiment would have been 39.4 calories per square meter per hour, and heat elimination only 30.8 calories. This shows again that the return to initial temperature is accomplished by heat saving rather than by increased heat production.

The results herein reported have shown that acetylsalicylic acid, like other antipyretic drugs, exerts its temperature reducing action essentially by increasing the processes of heat elimination. While stimulation of the metabolism is not seen, as in health, there is at least no depression at all comparable in extent to the increase in heat dissipation.

This action of acetylsalicylic acid is exhibited in afebrile stages and during convalescence, with resulting subnormal temperatures. It is not allowable, therefore, to state that antipyretics reduce an elevated but not a normal temperature; a more correct formulation of the facts is that *antipyretics reduce the body temperature in fever cases (including temporarily afebrile and convalescent phases) but not in normal persons.*

#### SENSITIVITY TO ANTIPYRETIC ACTION

What is the essential cause of this sensitivity to antipyretics on the part of persons who are or have recently been febrile? Its occurrence with normal initial temperatures is fundamentally disturbing to the hypothesis that the febrile state is one of "depression" of the heat regulating mechanism which antipyretics tend to overcome by a "stimulating" action, healthy individuals being, of course, insusceptible to such stimulation. The reinstating of a normal temperature might, it is true, be regarded as a manifestation of stimulation of the heat regulating mechanism, but diversion to a subnormal temperature must be given some other interpretation.

In seeking for a more satisfactory explanation of sensitivity to antipyretics, due consideration must be given to the factor of inanition. This condition is common to fever, afebrile intermissions and convalescence. Is it justifiable to assume that antipyretics will not reduce temperature if a supply of readily combustible material be available? This condition obtains in health but not in inanition, the stores of glycogen having been exhausted. To establish this hypothesis would require the demonstration that antipyretics arouse an excess heat elimination in both health and fever, acting against which a "chemical regulation," e. g., heat production from carbohydrates, would serve to prevent a change in the temperature level. Since, however,

TABLE 3.—RESULTS OF ADMINISTRATION OF ACETYLSALICYLIC ACID IN FEVER CASES

Subject	Date	C.c. per Minute				Respira- tory Quo- tient	Per Square Meter per Hour				Body Temperature		Pulse Rate	
		Carbon Dioxid Production		Oxygen Absorption			Calories Produced		Calories Eliminated		Change, C.	Initial, C.	Change per Min.	Initial per Min.
		Control	Acetyl- salicylic Acid	Control	Acetyl- salicylic Acid		Control	Acetyl- salicylic Acid	Control	Acetyl- salicylic Acid				
J. D.	1-24	...	161	...	202	0.80	...	38.7	...	54.4	-0.95	37.41	-14	70
	2-1	173	170	214	...	0.81	41.2	...	35.1	...	+0.41	37.20	+ 4	73
	2-26	...	170	...	193	0.88	...	...	...	...	-0.78	37.24	-12	80
G. G.	3-1	...	201	...	224	0.89	...	43.2	...	61.0	-1.07	38.41	- 8	108
	3-5	193	...	210	...	0.92	40.5	...	36.8	...	+0.21	38.27	- 6	108
	3-7	...	177	...	193	0.92	...	37.1	...	51.4	-0.80	37.20	- 2	85
G. M.	1-15	...	151	...	169	0.89	...	41.3	...	45.2	-0.41	37.69	-54	128
	1-16	153	...	181	...	0.85	43.4	...	41.0	...	+0.24	37.60	-11	100
	3-12	159	...	191	...	0.83	35.7	...	38.0	...	-0.14	37.75	0	88
T. W.	3-14	...	167	...	184	0.91	...	34.8	...	48.2	-0.83	37.75	- 4	84
Average Change	....	....	....	....	....	....	40.2	38.82 -3.5%	37.73	52.13 +38.2%				

it has been shown that heat elimination is not stimulated, by the antipyretic drug here tested, in normal persons, the hypothesis cannot stand in the form just stated. It was, nevertheless, considered of interest to determine whether or not the administration of dextrose with acetylsalicylic acid would tend to counteract the antipyretic action.

The result of giving 30 gm. dextrose with 1 gm. acetylsalicylic acid to a fever patient has been published elsewhere.<sup>9</sup> An unexpectedly profound fall in temperature (2 C. in two and one-half hours) took place. This exceeds by nearly 100 per cent. all effects noted from acetylsalicylic acid alone (Table 3), and soon led to the discovery that dextrose alone may exhibit antipyretic properties. Readily combustible material therefore is not necessarily a protection against the action of antipyretic drugs.

The dextrose work has led to a consideration of antipyretic action from the standpoint of the carbohydrate metabolism. Bearing on the question in hand is the effect which acetylsalicylic acid appears to exert, in fever cases but not in normal individuals, on the respiratory quotient. If it is true, as appears from the results described in this paper, that the drug causes an increased combustion of carbohydrates in fever patients and not in health, this fact may be of much significance in connection with the different response of the heat regulating mechanism in the two cases. It is necessary to develop this subject by further work.

#### CONCLUSIONS

1. Acetylsalicylic acid, in 1 gm. doses, which have no such action in normal persons, exhibits a marked antipyretic effect in febrile, temporarily afebrile and convalescent subjects.
2. In one and one-half hours the temperature change averaged  $-0.81$  C. in six experiments on four individuals, as against an average rise of  $0.18$  C. on four control days.
3. In the control experiments the heat elimination averaged 37.7 calories per square meter per hour. Under acetylsalicylic acid it became 52.1 calories, an increase of 38.2 per cent. The antipyretic effect is due essentially to this change, which is associated with marked perspiration and subjective warmth.
4. The fall in temperature was accompanied by a heat production of 38.8 calories per square meter per hour, a decrease of 3.5 per cent. below the 40.2 calories of the control days. This change is probably merely the result of the cooling of the body.
5. The drug caused an averaged decrease in the pulse rate of ten beats per minute. Temporary cardiac disturbances were noted in two cases.

9. Barbour, H. G.: *Proc. Soc. Exper. Biol. & Med.* **16**:136, 1919.

6. The return to the initial temperature level is brought about essentially by a reduction of the heat elimination to about one half of the normal figure and is unaccompanied by shivering or marked increase in carbon dioxid output.

7. Sensitivity of febrile, temporarily afebrile and convalescent subjects to antipyretics is not yet explained. These drugs do not "stimulate" a "depressed" heat regulating mechanism, nor is sensitivity due to a lack of readily combustible material (dextrose); but the respiratory quotient of antipyretic sensitive individuals appears to be increased by doses of acetylsalicylic acid which do not affect the quotient of normal persons. Further studies of the carbohydrate metabolism may elucidate the question of sensitivity.

The present series of investigations has been made possible by the friendly assistance of Dr. Francis G. Benedict. He has given most generously of his time and advice, besides placing much material at my disposal. Dr. Carpenter and Miss Johnson of the Carnegie Nutrition Laboratory have also contributed many valuable suggestions. The best cooperation possible has been given by Dr. Cox, superintendent, and the members of the medical, surgical and dietetic staffs of the New Haven Hospital and especially by Dr. George Blumer.

Miss S. B. Plant, laboratory assistant, has given painstaking care to the many routine duties connected with the manipulation and upkeep of the apparatus and has made all of the calculations.

To all of these the author takes pleasure in expressing sincere thanks.

## MENTAL DISORDERS FOLLOWING INFLUENZA \*

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PHILADELPHIA

Infection and intoxication are morbid processes which are undeniably the fundamental causes of abnormal mental functioning in a large group of cases. It has been sufficiently demonstrated that endogenous and exogenous toxic substances are apt to create products fit only for elimination, but not for cellular life; and that their contact with nerve elements exercises an obnoxious influence on the function of the latter.

The function of the brain may also be disturbed by bacterial poisons which engender microbic and cellular toxins. Although the precise action of the latter on the nerve cell is still somewhat obscure, nevertheless, its existence is a matter of daily observation. What is absolutely certain in this entire problem is the fact that the organism always endeavors to get rid of the exogenous, endogenous and bacterial poisons either through the kidneys, lungs, salivary and cutaneous glands by direct elimination, or by means of modification and complete destruction by the cells of various tissues and organs, including the endocrine glands. Not infrequently amelioration of mental disorders runs parallel with the proper functioning of these defense organs when their activity is rendered energetic and prompt.

In the present contribution reference will be made to one of those infectious processes which, after the acute phase had subsided, produced evidently very profound disturbances in the higher functions of the cerebrum, thus corroborating the theory of pathogenesis given in the foregoing paragraph. A further evidence is furnished, moreover, by the fact that close therapeutic attention to the various glands and organs was followed by satisfactory results.

The following study is based on a series of sixty-two cases all seen at the end of the febrile period during the phase of asthenia which ordinarily follows infectious diseases. The majority of the cases (forty-four) presented the well known confusional type of psychosis, more or less pronounced. The mental manifestations were particularly marked in individuals whose previous medical histories either suggested various episodic phenomena of a neuropathic character or contained accounts of actual psychotic disorders. This particular group differed greatly from the groups of cases without previous nervous or mental disorders. Each group deserves a separate description.

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\* Read before the Philadelphia Psychiatric Society, March 14, 1919.

*A. Cases With a Previous History of Psychopathic Traits.*—The physiognomy of the patient is expressionless. The look is vague and cannot be fixed on any one object. The patient is entirely oblivious of his surroundings. He does not answer when spoken to, and when urged he will repeat the last word or sentence of the question. Then the speech is very slow. Memory is vague. Some patients could not tell their age, and whether they had families or not. They were very docile and could be led without the least objection or resistance.

Several patients presented delirium with hallucinations. These occurred only occasionally, and there was some systematization in the delusional conceptions, but the systematization was imperfect. The delusions were either of a hypochondriacal, or persecutory character. The delirium occurred in sudden outbursts, and disappeared suddenly. It was particularly observed in individuals with a previous history of acute or chronic alcoholism, and was invariably associated with hallucinations. The latter were auditory and visual, and mostly of a terrifying nature. As in other delirious states, the hallucinations were fleeting and changeable in their composition. The delusional conceptions likewise did not possess a fixed character. All the ideas of the patients were in a state of chaos without a trace of associative processes, and consequently the memory was very poor, especially with regard to recent events.

A highly interesting picture was presented by one patient in whom the struggle between the manifestations of an expansive state and the inability to associate ideas was most manifest. At one time he was greatly exalted, spoke or rather would commence to speak of his great accomplishments, but incoherence and confusion promptly interrupted his train of thought; he rapidly broke down and became morose and quiet. This interruption occurred invariably when he attempted to recite his great deeds in the line of banking. It was evident that the confusion of ideas was the fundamental disturbance, and it was so profound that it interfered not only with the expression of thoughts, but with the expression of the emotions, this being evident also in the attitude and demeanor as well as the facial expression of the patient. It also gave color to the changes in the physical reactions. The digestive functions were most capricious; at times, they were most excellent, at others, very poor; constipation alternated with diarrhea. At times the muscular system presented hypotonia and sometimes hypertonia. In the first case there was a general relaxation so that station was difficult, the arms hung alongside the body; the face was without expression and saliva ran out of the mouth. In the second case there was hypertonia in the form of catatonic manifestations. Vasomotor

disturbances were present (erythemata), but they were of a variable character. The tendon reflexes were invariably increased.

*B. Cases Without Morbid Previous Histories.*—While the confusional element was present in these cases also, it was not so intense as in the previous group. The patient presented a physiognomy without reactions, but he frequently could be raised out of his confusional state when under the influence of some stimulating factor. However, this was transitory and the patient rapidly returned to his fundamental condition.

This group of cases differs also from the first group in that at no time during the entire course of the disease, hallucinations were present. It corresponds to Kraepelin's "asthenische Verwirrtheit" in contradistinction to the "halluzinatorische Verwirrtheit" of Meynert which covers the first group of cases. Besides the absence of hallucinations and the slight intensity of the confusion in the second group, the course of the affection was different in the two series of cases. In the first group the confusional state was protracted; in some patients who had before pretended similar outbreaks, the present attack was more pronounced than all previous ones. Both groups of cases presented various degrees of intensity, but it was especially in the first series that several varieties occurred. There was present in some of these cases a hallucinatory confusional state of a depressive character without systematization in the vague delusions or else with systematization. There were also cases of confusion with agitation, with and without delusions; finally cases occurred without hallucinations.

The second group of cases were all identical in their essential characteristics, the difference lay only in the degree of confusion and difficulty in associating ideas.

*Unusual Features of Other Cases.*—The remaining (eighteen) cases of the entire series of the present study were especially instructive by reason of some unusual features. In each of them the most conspicuous symptom was *amnesia* of a pronounced character. Every one of them had great difficulty in recalling names of important places and persons, or names of nearest relatives; some of them could not tell the number of their children, some did not know the days of the week, let alone the date, month and even year. With regard to the year, in some cases the error was as much as twenty years difference. Some patients could not recall even facts which had occurred almost immediately before being questioned, such as having taken food, as having read a newspaper, etc. They were all conscious of their amnesia, and made an effort to correct the defect and recall the forgotten facts, but in vain. At no time until the phase of improvement commenced, could they bring back to memory events in which they

participated even when attempts were made to aid them in their efforts by associating the forgotten facts with ideas which had a bearing on them.

In addition to the amnesia which was the most prominent symptom in this small group of cases, we should add that the entire mental attitude of the patients was that of individuals who are recovering from a protracted disease. There was a *mental asthenia*, so to speak. It was a tremendous effort for them to think, to respond to questions, to comprehend what was said to them. The mental strain which they were undergoing was visible in their facial expression, in their movements, and general behavior. It seems that the above mentioned inability of recalling facts was closely connected with and dependent on the asthenia. Just as it was difficult for them to associate ideas and reflect while being interrogated, so it was difficult for them spontaneously to bring back to memory facts and events. The amnesia, therefore, was merely a manifestation of the cerebral asthenia.

It was interesting to observe that when amelioration of condition commenced to make its appearance, a parallel and proportionate improvement was observed in all the manifestations, that is in the amnesia, etc. As memory is normally dependent on the facility of associating former impressions at any desired moment, loss of memory or deficient memory is in intimate relation with the loss of that capacity. As the cerebral asthenia of the patients was manifested in a difficulty in all mental operations, the amnesia was the natural result. The amnesia, therefore, could not be considered as having an independent existence, but only as one of the manifestations of a general cerebral condition caused by a post-infectious toxic state.

To recapitulate: Of the mental states observed in this series of cases one may mention three varieties: (A) a profound confusional psychosis with delusions and hallucinations; (B) a mild confusional state without hallucinations, but with illusional conceptions, and (C) cerebral asthenia with conspicuous amnesic phenomena.

#### CLINICAL COURSE

The course of these three conditions is not without some interest. In the first group a small number recovered (three), and the recovery was rapid; but the others are still under observation. They present alternating periods of improvement and of return to the original condition, and apparently show no tendency to recovery. The non-hallucinatory type presents a more promising outlook than the hallucinatory form; the amelioration of the symptoms being more evident and their intensity less pronounced. The above mentioned three recoveries occurred in cases which did not present hallucinations.

In the second variety of confusional psychosis in the series, while the symptoms were less intense than in the first, the cases nevertheless presented a longer duration than the three cases of the first group which made a recovery. The amelioration in the mental condition ran parallel with the improvement in the general physical state of health. The course of the psychosis was exceedingly slow, and for some time after the confusional element had disappeared there remained a certain degree of weakened attention and the exercise of the intellectual functions remained somewhat difficult. Eventually, however, the latter disappeared and the recovery was complete.

The last group of cases in the series which presented amnesia was composed of the asthenic cases. Their course resembled largely that of the previous group. The improvement in the memory coincided with the amelioration in other mental functions, and both ran parallel with the condition of the general asthenia. Simultaneous improvement and eventual recovery took place in all directions. The recovery was somewhat more rapid than in the second group of cases.

#### CONCLUSIONS

The observation made in the last two groups, concerning the parallel course of the various manifestations in the mental sphere and of those in the physical condition, also the parallel improvement, suggest at least a relationship between both groups of phenomena. On the other hand, the circumstances under which confusion ordinarily occurs, namely, in infections and intoxications, especially of internal origin, warrant the assumption that the nutrition of the cerebral neurons is altered by the altered composition of the body fluids which necessarily occurs in toxic states. That microscopic changes may take place in the cortical cells during a confusional state caused by toxic substances irrespective of their origin, had been demonstrated by Ballet. In the confusional psychosis which accompanies multiple neuritis and which is known under the name of Korsakoff's psychosis, he found cell changes in the cortex, namely, tumefaction and deformities, chromatolysis and disappearance of the nuclei (*Sem. méd.*, p. 284, 1898). This organic basis is logically applicable to the incurable cases. In the milder and curable ones we may suppose that the toxins produce a transitory functional disorder in the cells which promptly disappears, so that the cells rapidly recover their normal function. But it is to be assumed that both the functional and organic disorders of the cells are the result of intoxication. The latter may be observed in any of the infectious processes, of which influenza is one.

## THE ELECTROCARDIOGRAM AND VENTRICULAR PREPONDERANCE \*

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AND

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Following Einthoven's<sup>1</sup> first description of the characteristic directional changes in the R wave, in lead III, associated with aortic or mitral disease, the applicability of the electrocardiograph to the study of alterations in the size of the heart has been severely questioned. Clinical observers have held widely differing views in regard to the value of the so-called electrocardiographic signs of hypertrophy. That there are many cases in which the electrocardiograms do not agree with the clinical evidence has been recognized. Bridgeman<sup>2</sup> has called attention to the fact that in general the English and American observers have accepted the electrocardiographic evidences of hypertrophy, while the German authors placed but little reliance on these findings.

Classification of this mass of conflicting evidence began with the calculation of the direction of the electrical axis of the heart by Einthoven, Fahr, and de Waart.<sup>3</sup> These authors find that in normal individuals the electrical axis of the heart roughly corresponds to the anatomic axis at an angle between 40 and 90 degrees from the horizontal. Somewhat comparable changes occur in the two axes on mechanical displacement of the heart by change in posture, the greatest difference in the electrical axis being between the right-sided and left-sided prone positions. Lesser differences are noted between the upright and horizontal. The greatest mechanical changes in the electrical axis of the heart are those due to the respiratory movements for the angle  $\alpha$  increases with inspiration and decreases with expiration, the degree of change varying between 5 and 30 degrees. Waller<sup>4</sup> reports similar variations in the axis, though he considers the normal to show a greater range of variability, i. e., from 10 to 100 degrees with 60 degrees considered as the typical angle.

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\* From the Cardiographic Department of the Johns Hopkins Hospital and University.

1. Einthoven, W.: *Arch. internat. de physiol.* **4**:132, 1906.

2. Bridgeman, E. W.: *Arch. Int. Med.* **15**:487 (April) 1915.

3. Einthoven, W., Fahr, G., and de Waart, A.: *Arch. f. d. ges. Physiol.* **150**:275 1913.

4. Waller, A. D.: *Proc. Roy. Soc. Lond.* **138**: B, 49 1914.

In his interpretation of the meaning of these differences in the electrical axis of the heart, Waller<sup>5</sup> contents himself with a classification into those hearts with a vertical and those with a horizontal axis. These two types he speaks of as the vertical or youthful heart and the horizontal or drop heart and considers them as more or less identical with the same types observed roentgenographically. Einthoven, Fahr and de Waart, however, believe that the study of the electrical axis of the heart is of definite clinical value, and postulate that when the degree of change from the normal is too great to be explained by simple anatomic displacement, the explanation must be sought for in a hypertrophy of the corresponding ventricle.

Lewis,<sup>6</sup> in attempting to apply the Einthoven criteria of hypertrophy, clinically, was struck by the discrepancies between the electrocardiographic and the clinical evidence; a condition that led him into a careful study of cardiac hypertrophy. By an exact record of ventricular weights he was able to point out not only the inaccuracies of the ordinary clinical signs of ventricular hypertrophy but also the impossibility of judging ventricular preponderance at the post-mortem table with any reasonable degree of accuracy. More important still, in those cases in which complete data were available, he was able to point out the close relationship between the electrocardiographic findings and the ventricular weights. Concluding, Lewis<sup>7</sup> emphasizes the fact that the electrocardiogram gives evidence not of hypertrophy of the heart as such, but rather of preponderance of one ventricle or the other.

"The point which it is desired to emphasize is that the term preponderance is employed irrespective of the weight of the whole heart. . . . It is an altered (weight) ratio (between the two ventricles) and that alone which conditions the form of the electrocardiograms to be described."

In this study of ventricular hypertrophy, Lewis made use of an arbitrary formula in determining the degree of electrical preponderance. This formula has recently been amplified by White and Bock<sup>8</sup> in an effort to secure a quantitative measure of the degree of preponderance. Their index is determined according to the formula:

$$(U_1 + D_3) - (D_1 + U_3) = \text{Index}$$

U equals the amplitude of the chief upward excursion of the QRS group of the corresponding lead.

D equals the amplitude of the chief downward excursion of the QRS group of the corresponding lead. White considers an index of

5. Waller, A. D.: *Proc. Roy. Soc. Lond.* **136**: B, 507, 1913.

6. Lewis, T.: *Heart* **5**:367, 1914.

7. Lewis, T.: *Clinical Electrocardiography*, London, 1919, p. 30.

8. White, P. D., and Bock, A. V.: *Am. J. M. Sc.* **156**:17 (July) 1918.

+ 20 or over as indicative of a left ventricular preponderance, while an index from - 15 to - 18 or more is characteristic of a right ventricular preponderance.

In a recent article from this laboratory<sup>9</sup> we have drawn attention to a graphic method for the rapid and accurate determination of the inclination of the electrical axis of the heart. We find this to be the most accurate method for the quantitative determination of ventricular preponderance. In brief, measurements are made of the RS wave in each of the different leads. Then, on the general assumption that the deflection represents the resultant of opposing or balanced electrical currents from the two sides of the heart, the net movement of the string is determined by subtraction of the downward deflection in each lead from the upward. These measurements and the basic assumption are the same as those that underly the determination of the index of Lewis or White. However, instead of the calculation of an index by the total movement of the galvanometer string, the net deflections in leads I, II and III are used to reconstruct the Einthoven triangle and to determine graphically the direction of the electrical axis in the heart. This reconstruction gives not only  $\alpha$ , but the manifest value of the potential difference (E) as well. It is in ignoring this latter point that the White index becomes theoretically unsound, for the potential change observed in any lead of the electrocardiogram depends on both the total potential difference in the heart (E) and the direction of the electrical axis  $\alpha$ . Theoretically, for any given value of E the White index would be greatest when  $\alpha$  equals - 30 or + 150 degrees, while when  $\alpha$  equals + 60 degrees the index would be zero regardless of the size of E. According to the normal limits stated by White, a left ventricular preponderance is indicated when  $E = 11.5$  if  $\alpha = - 30$  degrees, but if  $E = 23$ , then an equal degree of preponderance is indicated though  $\alpha = + 30$  degrees. Similarly, when  $\alpha = + 150$  degrees a right ventricular preponderance is not indicated unless E is at least 8.6 while at + 90 degrees a value for E of 17.3 or more would nevertheless show ventricular change. Our greatest difficulty in the use of the White index has not been that of false indications with great potential differences in the heart but rather with the prevalence of such small values of E that positive change in the index was impossible regardless of  $\alpha$ . In such cases the ventricular preponderance can only be determined by a calculation of the direction of the electrical axis.

The present series of cases of ventricular preponderance were secured in the course of about 200 routine examinations made in the

9. Carter, E. P., Richter, C. P., and Greene, C. H.: *Bull. Johns Hopkins Hosp.*, **30**:162 (June) 1919.

cardiographic department of the Johns Hopkins Hospital. For the most accurate determination of  $a$  the records in the different leads should be synchronized to avoid phasic variations between the several derivations. Measurements should also be taken at identical periods in the respiratory cycle. Such refinements of technic were not possible in the present instance, nor are they desirable, except in physiologic experimentation of the greatest exactitude.

As a routine procedure, the measurements of several successive peaks were averaged in order to secure a mean value of  $a$  independent of possible respiratory variation. Usually, such measurements obeyed the Einthoven law ( $E_1 + E_3 = E_2$ ) or else the error due to phasic differences between the three leads was so slight as to permit of the selection of a mean value of  $a$ . In those few cases in which marked discrepancy existed,  $a$  was determined from the measurements in leads I and III, lead II being ignored. When determined in this manner, the values of  $a$  are accurate to within 5 degrees in all cases except those showing the most pronounced phasic variation. A greater degree of accuracy is unnecessary in ordinary clinical routine though it is desirable to secure values closer than the 60 degrees approximations secured by simple inspection as pointed out by Pardee.<sup>10</sup>

We have arbitrarily chosen 0 and +90 degrees as representing the extremes of the normal values of  $a$ . While these limits were set largely as a matter of convenience and are slightly greater than those of Einthoven, Fahr, and de Waart, they nevertheless lie within the normal values of Waller. In view of the present uncertainty of the exact dividing line between normal and pathologic hypertrophy, especially of the left ventricle, these values may be considered to be sufficiently accurate to serve for the present.

Table 1 shows the electrocardiographic findings in this series as compared with the physical findings and the clinical impression. Examination shows that there is no relationship between the degree of ventricular preponderance and the limits of the relative cardiac dulness. In all of these cases the great variability and consequent nonreliability of the White index is to be pointed out.

As a means of accurate measurement and diagnosis of cardiac size and position, the percussion of the relative cardiac dulness has more recently given way to the orthodiagram and the teleroentgenogram. That these roentgenographic methods fail to give an insight into the question of the preponderance of the ventricles is shown in Table 2. Bardeen,<sup>11</sup> in a recent exhaustive study of the teleroentgenogram, points out that owing to the differing positions of the heart within

10. Pardee, H. E. B.: J. A. M. A. **62**:1311 (April 25) 1914.

11. Bardeen, C. R.: Am. J. Anat. **23**:423 (March) 1918.

the chest, measurement of the cardiac borders fails to give a true impression of local changes in the heart. He does show, however, that the area of the cardiac shadow is a true index to hypertrophy of the heart as a whole. From the area of the shadow, Bardeen is able to calculate very accurately the cardiac volume and, though less accurately, the weight. It has been recognized that while the teleroentgenogram may give the best index to hypertrophy, it is nearly always

TABLE 1.—COMPARISON OF ELECTROCARDIOGRAPHIC AND PHYSICAL FINDINGS

Case No.	Electrocardiographic Preponderance		Relative Cardiac Dulness		Clinical Impression
	$\alpha^\circ$	White Index	Right, Cm.	Left, Cm.	
2240	— 5	+15.0	4.0	14.0	Aortic stenosis and insufficiency; hypertension; ascites
2242	— 5	+21.0	4.5	15.0	Myocardial insufficiency; hypertension; chronic nephritis
2245	— 5	+17.5	4.0	12.5	Aortic insufficiency; syphilis; right hydrothorax
2272	— 5	+ 9.5	4.0	15.5	Hypertension with dilatation; aneurysm of arch
2269	— 10	+10.0	5.5	17.0	Aortic insufficiency; myocardial insufficiency; endocarditis; syphilis
2345	— 10	+ 7.0	3.0	11.0	Aortic roughening; chronic myocarditis; arteriosclerosis; syphilis
2247	— 15	+11.5	4.0	11.5	Myocardial insufficiency; chronic nephritis; hypertension
2230	— 20	+17.0	5.0	17.0	Myocardial hypertrophy and insufficiency; hypertension
2360	— 25	+12.0	5.0	17.0	Myocardial insufficiency; hypertension; chronic nephritis
2222	— 30	+12.0	5.0	15.5	Aortic insufficiency; myocardial insufficiency
2243	— 30	+ 8.0	5.5	13.0	Myocardial insufficiency; hypertension; arteriosclerosis
2277	— 35	+20.0	5.0	17.0	Myocardial insufficiency with dilatation; colloid goiter
2374	— 45	+ 8.0	3.0	15.0	Myocardial insufficiency with dilatation; hypertension
2352	— 60	+ 8.0	4.0	....	Myocardial insufficiency; hypertension; syphilis
2255	—110	+ 6.5	5.5	15.0	Myocardial insufficiency; hypertension; chronic nephritis
2257	—140	— 9.5	4.5	15.0	Myocardial insufficiency; essential hypertension; arteriosclerosis
2375	+ 95	— 3.0	3.5	18.0	Myocardial insufficiency; atrial fibrillation
2271	+100	—16.5	3.5	7.5	Mitral stenosis and insufficiency; chronic endocarditis
2310	+105	—15.5	0.0	10.0	Right pneumothorax
2364	+105	— 5.5	4.0	12.0	Tuberculous peritonitis
2256	+115	— 5.0	5.0	15.0	Mitral stenosis and insufficiency; myocardial insufficiency
2275	+120	— 3.0	4.0	13.0	Myocardial insufficiency; hypertension
2291	+140	—11.0	5.0	12.0	Mitral stenosis and insufficiency; pericarditis; endocarditis
2331	+150	— 2.0	3.0	7.0	Tuberculous peritonitis; right pleurisy

silent in regard to the part played by the different chambers of the heart in this hypertrophy. Morison and White<sup>12</sup> have tried to throw light on this point by the use of oblique illumination and an estimation of the depth of the cardiac shadow. Any increase they believe to be an early and valuable sign of hypertrophy, especially of the left ventricle. Such results while valuable, however, lack the definiteness of the electrocardiographic indications.

12. Morison, J. M. W., and White, L.: Arch. Radiol. & Electroth. **23**:282 (Feb.) 1919.

The crucial experiment in such a study as the present is the direct comparison of the electrical axis with the ventricular weights, directly determined. Such a comparison is made possible by the experiments of Lewis<sup>6</sup> and of Cotton,<sup>13</sup> each of whom has published a short series of parallel determinations of the electrocardiogram and the ventricular weights. These results are shown in Table 3. In general, a very good agreement is evident between the degree of electrical preponderance indicated by the weight ratio. Three marked exceptions to this rule occur: Lewis, No. 109, and Cotton, Nos. 101 and 225. Of these three, the Lewis No. 109 presents a slightly peculiar electrocardiogram in that the measurements given indicate a practically diphasic RS curve in each of the three leads. The exact bearing of this rather peculiar type of curve cannot be explained in the light of

TABLE 2.—COMPARISON OF ELECTROCARDIOGRAPHIC AND ROENTGENOGRAPHIC FINDINGS

Case No.	Electrocardiographic Preponderance		Teleroentgenographic Measurements		Case No.	Electrocardiographic Preponderance		Teleroentgenographic Measurements	
	$\alpha^\circ$	White Index	Right, Cm.	Left, Cm.		$\alpha^\circ$	White Index	Right, Cm.	Left, Cm.
2253	— 5	+10.5	4.5	8.7	2235	— 30	+ 3.0	4.1	7.7
2340	— 5	+ 7.0	3.4	8.4	2233	— 35	+12.5	4.3	9.9
2347	— 5	+ 4.0	6.1	9.8	2226	— 35	+11.0	4.9	9.0
2208	—15	+ 6.0	4.1	8.3	2236	— 40	+28.0	4.5	10.5
2234	—15	+15.0	3.8	10.3	2237	— 40	+ 8.0	5.4	12.3
2247	—15	+11.5	4.0	9.0	2262	— 60	+15.0	5.0	10.4
2306	—15	+11.0	5.0	10.9	2255	—110	+ 6.5	5.0	11.5
2308	—15	+10.0	3.5	8.8	2313	+100	—10.0	3.2	7.3
2230	—20	+17.0	3.0	7.5	2364	+105	— 5.5	3.0	9.0
2251	—20	+12.0	2.5	10.0	2338	+115	— 9.0	2.3	9.6
2318	—20	+14.5	4.8	8.4	2372	+135	— 6.0	5.5	13.0
2252	—25	+26.0	5.4	9.7	2305	+150	—13.5	3.5	9.5
2336	—25	+12.0	5.6	13.3					

our present knowledge of the electrocardiogram. In the two cases reported by Cotton the graphic records were taken some time before death, and he suggests that change may have occurred in the interim. Stewart<sup>14</sup> has demonstrated in dogs, that changes in the ventricular weights may be found within a week after experimental lesions of the valves. In view of these experiments, the validity of Cotton's explanation may be assumed. If these three questionable cases are eliminated from the series, then the agreement becomes very close indeed. It was this agreement that led Lewis to emphasize the electrocardiograph as a means of determining the relative mass of the two ventricles.

Recently, in a preliminary report, Fahr<sup>15</sup> stated that the direction of the RS wave in the electrocardiogram is dependent on the

13. Cotton, T. F.: *Heart* **6**:217, 1917.

14. Stewart, H. A.: *J. Exper. M.* **13**:187, 1911.

15. Fahr, G. E.: *J. Mich. M. S.* **17**:10 (Jan.) 1918.

relative length of the conduction system and the consequent relative time of propagation of the excitation wave in the two sides of the heart. In continuation, he states the possibility in cases of dilatation, of calculating the directional relationships of the RS wave from measurements of the two branches of the bundle of His. According to Fahr, therefore, the electrocardiographic signs of preponderance are directly related to changes in ventricular volume rather than mass, and so indicate relative dilatation instead of relative ventricular hypertrophy as claimed by Lewis, and, as it seems to us, substantiated by the published cases of Lewis and Cotton (Table 3).

TABLE 3.—COMPARISON OF ELECTROCARDIOGRAPHIC AND NECROPSY FINDINGS

Author	Case No.	Electro-cardiographic Preponderance		Ventricular Weights, L — Ratio R	Pathologic Diagnosis
		$\alpha^\circ$	White Index		
Lewis	109	— 90	+ 1.5	1.38	Aortic disease with mitral stenosis
Cotton	265	— 70	+17.5	2.55	Renal disease
Lewis	110	— 60	+19.0	2.60	Angina pectoris
Cotton	147	— 30	+29.5	2.63	Renal disease
Cotton	225	— 25	+ 9.0	1.55	Renal disease
Lewis	2	— 10	+21.5	2.04	Aortic disease
Lewis	107	+ 5	+12.5	1.87	Aortic disease
Lewis	59	+ 25	+ 5.5	1.82	Mitral stenosis and aortic disease
Lewis	58	+ 30	+ 8.0	1.94	Renal disease
Cotton	236	+ 80	— 3.5	1.30	Mitral stenosis
Cotton	101	+ 85	—10.0	1.97	Renal disease
Lewis	60	+120	— 7.0	1.60	Mitral stenosis and aortic disease
Lewis	63	+135	—15.5	0.82	Mitral stenosis and atrial fibrillation
Lewis	...	+140	—77.0	0.41	Congenital pulmonary stenosis
Cotton	189	+170	— 6.0	0.82	Mitral stenosis

It is hoped that further evidence bearing on this point may be presented later, though in view of the close relationship existing between dilatation and hypertrophy in any long standing process, this exact differentiation is, after all, rather an academic question.

## SUMMARY

It may again be emphasized that the electrocardiogram is the only satisfactory clinical method capable of estimating the relative preponderance of the two ventricles. Combined with the teleroentgenogram as a guide to gross hypertrophy of the heart, it should furnish the clinician with an increased insight into the question of the mechanics of cardiac response in cases of hypertrophy.

In view of the ease of determination of the inclination of the electrical axis of the heart it is hoped that further work may be stimulated with a view to deciding its value as a quantitative guide to cardiac change.

# THE BASAL METABOLISM IN EXOPHTHALMIC GOITER \*

J. H. MEANS, M.D., AND J. C. AUB, M.D.

BOSTON

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## INTRODUCTION

Four and one half years ago a study of the basal metabolism in exophthalmic goiter was started at the Massachusetts General Hospital. Preliminary reports on this work appeared in June, 1916,<sup>1</sup> and in July, 1917.<sup>2</sup> It was impossible for us at the latter date, because of the imminence of mobilization, to present more than the barest outline of our work, together with the conclusions drawn to that time.

The original program of the research was to follow the metabolism and clinical condition of a series of cases of exophthalmic goiter over a period of several years, during which time the patients would be undergoing therapy of one sort or another. This was carried out to

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<sup>1</sup>From the Medical Service of the Massachusetts General Hospital and the Medical Department of the Harvard Medical School, aided in part by a grant from the Proctor Fund, Harvard University.

1. Means, J. H.: Studies of the Basal Metabolism in Disease, Boston M. & S. J. **174**:864 (June 15) 1916.

2. Means, J. H., and Aub, J. C.: Study of Exophthalmic Goiter from Point of View of the Basal Metabolism, J. A. M. A. **69**:33 (July 7) 1917.

the end of April, 1917. Then, during the two years of the war, the patients, for the most part, disappeared from observation, although nine were seen once during that time.<sup>3</sup> Since our discharge from the service in March, 1919, we have made every effort to locate these patients and to get them to the hospital for further observations. Of the total cases of toxic goiter, fifty-five in number, which comprised the original series, nine patients are known to be dead, twenty-four have recently had basal metabolism determinations, ten more have been seen or heard from, and twelve are lost.

The purpose of the present paper, then, is twofold: in the first place, we wish to present in full the data that we outlined in previous papers, and secondly, to present and discuss the data recently secured. Our discussion is based on 345 metabolism observations on 130 patients.

#### HISTORICAL

For the purposes of this paper, an exhaustive résumé of the literature is not necessary.

On the subject of the gas exchange in thyroid disease, the German literature, beginning with Magnus-Levy,<sup>4</sup> is voluminous; the American literature is scanty. DuBois<sup>5</sup> unquestionably is the pioneer in this country, and in his paper a review of the German literature will be found. Following DuBois we,<sup>1, 2</sup> also Boothby,<sup>6</sup> and very recently McCaskey,<sup>7</sup> have emphasized the importance of basal metabolism determinations as an index of toxicity in hyperthyroidism.

We believe that our own work is the first in this country in which the metabolism of patients with exophthalmic goiter has been followed before treatment, and for periods of two or more years after treatment.

It would obviously be out of place to discuss the vast literature of the surgery or of the roentgen-ray treatment of the thyroid. An account of the early work in roentgen-ray treatment of exophthalmic goiter at the Massachusetts General Hospital has been published by Seymour.<sup>8</sup>

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3. These observations were kindly made for us by Dr. Harry Linenthal, assisted by Miss Catherine Thacher.

4. Magnus-Levy, A.: *Gaswechsel bei Thyroidea*, Berl. klin. Wchnschr. **32**: 650, 1895.

5. DuBois, E. F.: *Metabolism in Exophthalmic Goiter*, Arch. Int. Med. **17**: 915 (June) 1916.

6. Boothby, W. M.: *Clinical Value of Metabolic Studies in Thyroid Cases*, Boston M. & S. J. **175**:564 (Oct. 19) 1916.

7. McCaskey, G. W.: *The Basal Metabolism and Hyperglycemic Tests of Hyperthyroidism with Special Reference to Mild and Latent Cases*, J. A. M. A. **73**:243 (July 26) 1919.

8. Seymour, M.: *Treatment of Graves' Disease by the Roentgen Rays*, Boston M. & S. J. **175**:568 (Oct. 19) 1916.

The whole subject of the relation of the thymus gland to exophthalmic goiter has been set forth by Halsted in a Harvey Lecture.<sup>9</sup> Halsted predicts that for roentgen-ray and radium treatment there is a great future, particularly because of the important rôle of the thymus in the causation of exophthalmic goiter, and the profound effect of irradiation on that gland. Other writers, Boggs<sup>10</sup> for example, have reported good results with the roentgen ray, especially when the thymus gland is exposed as well as the thyroid.

#### METHODS

The methods used will merely be mentioned, having been described and discussed in previous papers.<sup>1, 11, 12</sup>

The gas exchange of normal individuals resting, and in the post-absorptive condition, has, with certain recognized variations due to age and sex, been found to be very constant if expressed in terms of their body surface.<sup>13, 14</sup> The gas exchange of patients with hyperthyroidism, on the other hand, is elevated above the normal. We have used the degree of elevation as a measurement of the degree of thyroid intoxication.

The basal gas exchange was determined with the Benedict universal respiration apparatus, and the heat production was calculated therefrom. Through April, 1917, we used the calorific value of oxygen for the respiratory quotient obtained; in those calculations after that time we determined oxygen only and assumed an R. Q. of 0.82.

The body surface was determined from DuBois' height weight chart,<sup>15</sup> except in a few instances early in the work, where the linear formula<sup>16</sup> was used.

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9. Halsted, W. S.: Significance of the Thymus Gland in Graves' Disease, Harvey Lectures, 1913-14, p. 224.

10. Boggs, R. H.: Treatment of Goiter by Roentgen Rays, Interstate M. J. **24**:362 (April) 1917.

11. Palmer, W. W.; Means, J. H., and Gamble, J. L.: Basal Metabolism and Creatinin Elimination, J. Biol. Chem. **19**:239, 1914.

12. Means, J. H.: Studies of Basal Metabolism in Obesity and Pituitary Disease, J. M. Research **32**:121, 1915.

13. Means, J. H.: Basal Metabolism and Body Surface, J. Biol. Chem. **21**:263, 1915.

14. Gephart, F. C., and DuBois, E. F.: Basal Metabolism of Normal Adults with Special Reference to their Surface Area, Arch. Int. Med. **17**:902 (June) 1916.

15. DuBois, D., and DuBois, E. F.: Formula to Estimate Approximate Surface Area, Arch. Int. Med. **17**:863 (June) 1916.

16. DuBois, D., and DuBois, E. F.: The Measurement of the Surface Area of Man, Arch. Int. Med. **15**:868 (June) 1915.

The roentgen-ray treatments were given at the Massachusetts General Hospital by Drs. G. W. Holmes and A. S. Merrill and we understand that they will publish an account of the work from the point of view of the roentgenologist with full particulars as to methods. The thyroid and thymus glands were both exposed at each treatment to nearly the maximum dose the skin would stand. The treatments were given from three to four weeks apart, as a rule, though sometimes a longer gap would occur.

The surgical operations, unless otherwise stated in the tables, were performed by Dr. C. A. Porter at the Massachusetts General Hospital. Almost without exception, the operations consisted in either ligation of the superior vessels or in partial thyroidectomy. The word lobectomy as we have used it in the tables indicates a partial thyroidectomy.

#### CLINICAL AND METABOLISM DATA

Our work is set forth in a series of tables. These, though voluminous, have been purged of all but essential data.

In the matter of figures, we have endeavored to give as few as possible. In case two figures are derivable, one from another, but one has been shown. Thus, the patient's age, sex, height and weight are given, but his surface area is not. If anyone wishes the area he has but to turn to DuBois' chart.<sup>15</sup> The oxygen absorption not being interesting per se is omitted, but the calories per square meter per hour, which are derived from it, are shown. The carbon dioxid and respiratory quotient are not given, because they do not enter directly into the present problem. They may be published later. In all periods used the quotients were within normal limits.

To determine the variation from the normal metabolism we have used the standards, which have been adopted by the Russell Sage Institute,<sup>17</sup> which take into account the variations due to age and sex. Our figure for the variation of the metabolism from the normal is the percentile variation above or below (expressed by + or —) the appropriate one of these standards. The really essential figures for purposes of discussion are the percentile variation from the normal metabolism, the pulse rate and the body weight.

We will now proceed with a running account of the material contained in the several tables, adding such clinical notes as the occasion seems to demand and later we shall analyze the data contained therein.<sup>18</sup>

17. Aub, J. C., and DuBois, E. F.: Basal Metabolism of Old Men, *Arch. Int. Med.* 19:823 (June) 1917.

18. In the text and in the tables all patients are referred to by our laboratory numbers. They were referred to by the same numbers in our earlier paper, and will be in future papers, hence can readily be identified.

*Controls.*—Normal controls have appeared in earlier papers. A certain number of pathologic controls have likewise been obtained. In Table 1 are collected the data on twenty-two such cases, together with that of three normals (Nos. 7, 43 and 44). We do not pretend, of course, that alterations in the metabolism are confined to thyroid disease. It is a well known fact that they occur in other ductless gland disturbances and in blood diseases, also in acidosis and fever. Table 1 is interesting, however, in that it shows a variety of abnormalities in which there is little, if any, variation from the normal. Two cases of neurasthenia (Nos. 1 and 119) and one of a psychoneurosis (No. 109) all vary less than 10 per cent. from the normal. The same is true in such conditions as myasthenia gravis (No. 4), Raynaud's disease (No. 8), elephantiasis (No. 11), acroparesthesia (No. 14), Addison's disease (No. 20), and metrorrhagia (No. 69). A case of pernicious anemia (No. 17) and one of secondary anemia (No. 108) were also within normal limits. A rise is often found in pernicious anemia,<sup>19, 20</sup> but in our case, just mentioned, it will be noted that there was not a very severe degree of anemia at the time the observation was made. Two cases of tachycardia of unknown origin (Nos. 19 and 50) varied only 5 and 11 per cent., respectively, above the standard. A case of irritable heart (No. 158) was quite within normal limits. A case of paroxysmal tachycardia (No. 67) showed a definite elevation, and it is interesting to note that the elevation is greater during an interval than during a paroxysm. Two cases of obesity (Nos. 47 and 58) were quite within normal limits. This is additional evidence in favor of the view expressed by one of us (J. H. M.) in an earlier paper<sup>21</sup> that there is no fundamental change in the basal metabolism in obesity. An inactive acromegalic (No. 122) was also normal. Of two diabetics, one (No. 55) showed a normal figure, the other (No. 56) a slight reduction. This last patient, however, had been starving for over four days, so this reduction was quite what we should expect. A case of psoriasis in an elderly woman (No. 94) showed a rise of 12 per cent., and a case of pelvic inflammation and phlebitis (No. 124) showed a rise of 8 per cent., which is within the range of normal variation.

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19. Meyer, A. L., and DuBois, E. F.: Basal Metabolism in Pernicious Anemia, *Arch. Int. Med.* **17**:965 (June) 1916.

20. Tompkins, E. H.; Brittingham, H. H., and Drinker, C. K.: Basal Metabolism in Anemia, *Arch. Int. Med.* **23**:441 (April) 1919.

21. Means, J. H.: Basal Metabolism in Obesity, *Arch. Int. Med.* **17**:704 (May) 1916.

TABLE 1.—METABOLISM DATA. CONTROL CASES

No.	Date	Sex	Age	Weight, Kg.	Height, Cm.	Pulse	Calories per Square Meter per Hour	Percen- tile Varia- tion from Standard	Remarks
1	6/10/14	♂	22	63.2	185.5	88	41.2	+ 4	Neurasthenia
1	6/11/14	♂	22	63.2	185.5	79	39.3	0	
4	10/19/14	♂	22	38.3	.....	75	36.5	- 1	Myasthenia gravis
7	12/ 3/14	♂	60	69.3	.....	67	31.5	- 7	Normal
8	2/18/15	♂	40	56.7	165.0	74	35.5	- 1	Raynaud's disease
11	5/24/15	♂	18	55.0	157.5	84	36.4	- 4	Elephantiasis -
14	4/ 6/15	♂	60	65.0	150.0	67	35.1	+ 3	Acroparesthesia
17	4/20/15	♂	41	51.7	162.0	78	37.1	- 4	Pernicious anemia, Hg 70%, R. C. 2.9 mil.
19	4/26/15	♂	55	70.0	.....	98	39.3	+ 5	Tachycardia of unknown origin
20	5/ 6/15	♂	31	62.0	.....	62	42.0	+ 6	Addison's disease
43	11/18/15	♂	19	71.3	175.0	60	44.0	+ 7	Normal
44	11/19/15	♂	23	62.1	156.0	78	42.6	+15	Normal
47	12/18/15	♂	25	77.5	160.0	65	38.3	+ 3	Obesity
50	1/12/16	♂	32	54.0	172.5	105	43.8	+11	Tachycardia of unknown origin
55	2/18/16	♀	47	55.0	161.8	80	35.3	- 2	Diabetes not sug- ar-free, alveolar CO <sub>2</sub> 33.3 mm.
56	2/19/16	♀	36	49.5	162.0	59	31.2	-14	Diabetes sugar- free, 5th day of fast; alveolar CO <sub>2</sub> 29.4 mm.
58	4/ 1/16	♀	38	109.0	159.0	80	37.8	+ 4	Obesity and hyper- trophic arthritis
67	9/11/16	♀	50	59.4	166.8	176	42.0	+20	Paroxysmal tach- ycardia during paroxysm
67	9/11/16	♀	50	59.4	166.8	85	45.3	+29	P a r o x y s m a l tachycardia dur- ing interval
69	9/14/16	♀	18	56.3	161.0	87	37.2	- 2	Metrorrhagia
108	11/16/16	♀	46	56.8	164.0	101	38.5	+ 7	Secondary anemia
109	11/17/16	♀	32	46.0	158.2	93	38.6	+ 6	Psychoneurosis
119	12/ 5/16	♀	22	62.3	165.5	96	40.5	+ 9	Neurasthenia
122	12/10/16	♀	31	75.5	175.0	82	39.0	+ 7	Acromegaly, inac- tive
124	12/19/16	♀	40	67.5	168.0	91	38.9	+ 8	Phlebitis, pelvic inflammatory (subacute), glyco- suria
158	3/14/17	♀	20	45.0	163.5	77	38.8	+ 5	Irritable heart
94	10/28/16	♀	78	69.0	163.4	68	36.9	+12	Psoriasis

A more interesting collection of controls is shown in Table 2. This comprises cases with thyroid enlargement, but with no clear cut clinical evidence of thyrotoxicosis. The size and character of the goiter are indicated in the table, and under "Remarks," a statement of the general nature of the case is given. Of these seventeen cases, only two varied more than 10 per cent. from the standard (Nos. 91 and 92). Both these patients had tachycardia, and although very atypical, these may yet have been cases of mild exophthalmic goiter. In our first paper<sup>2</sup> we showed diagrammatically that the elevation in metabolism in thyrotoxicosis runs essentially parallel to the clinical evidence of intoxication. This table shows the corollary that patients with thyroid tumors, but with no definite clinical evidence of hyperthyroidism have no increase in their metabolism. In these seventeen

cases we have been able to secure follow-up data in only seven, but none of these seven have clinically developed any indication of exophthalmic goiter.

*Differential Diagnosis.*—Soon after the work on our series of exophthalmic goiter cases was started, we began to receive requests from clinicians for basal metabolism determinations for purposes of differential diagnosis in cases presenting suggestive symptoms. Such a group of cases is shown in Table 3. It will be worth while to spend a little time examining these.

Thirty-three cases are included in this table. Of these, twelve (Nos. 35, 46, 73, 74, 75, 80, 81, 103, 118, 146, 155 and 127) showed a variation of not more than 10 per cent. from the standard. Seven of these twelve patients have been seen or heard from this year, and none of them has developed exophthalmic goiter.

One case (No. 65) in which it was thought that prolonged irradiation might have produced hypothyroidism, showed a result 13 per cent. below the standard. This figure is somewhat suggestive of hypothyroidism, no doubt, but the patient, when seen this year, presented no clinical evidence of that condition.

Only three cases of this group showed a rise of more than 40 per cent. One of these (No. 159) was one of recurrent thyroid carcinoma. The metabolism result is interesting inasmuch as the only other thyroid carcinoma we have studied showed a reduction from the normal.<sup>22</sup> The next highest metabolism in this group is that of Case 147. This patient had a colloid goiter with suggestive symptoms. Unfortunately, in neither of these patients were we able to secure follow-up data. Case 112 is quite striking, for when first seen, no goiter or eye signs were present, but he had suggestive symptoms and the metabolism was 44 per cent. above normal. His later history shows that subsequently he developed true exophthalmic goiter.

Of the remaining seventeen cases showing a rise of anywhere between 10 and 40 per cent. above normal, eight have been lost. Four have subsequently developed exophthalmic goiter (Nos. 26, 84, 136 and 152). Two patients are now in good health (Nos. 116 and 153); one case (No. 78) seems to be rather of the effort syndrome class and two cases still remain in the doubtful class (Nos. 27 and 149).

We believe that our Tables 2 and 3 illustrate clearly the importance of metabolism determinations for purposes of differential diagnosis in cases of obscure thyroid disease. Table 2 shows that for the

22. Means, J. H., and Aub, J. C.: Basal Metabolism in Hypothyroidism Arch. Int. Med. 24:404 (Oct.) 1919.

TABLE 2.—METABOLISM DATA. PATIENTS WITH ENLARGED THYROID GLANDS BUT WITHOUT CLINICAL EVIDENCE OF HYPERTHYROIDISM

No.	Date	Sex	Age	Weight, Kg.	Height, Cm.	Pulse	Calories per Square Meter and Hour	Per- cent Vari- ation from Stand- ard	Thyroid			Duration of Goiter	Remarks	Patient's Condition in Spring of 1919
									Degree En- lar- ge- ment	Character	Bruit			
13	3/27/15	♀	30	56.0	158.0	82	40.0	+10	++	Soft, smooth, symmetrical	0	10 years	Symptoms of toxemia at onset; perfectly well for several years	Remained in good health; has married and had twins
15	4/ 9/15	♀	14	37.5	150.0	81	44.5	+ 3	+	Soft, smooth,	0	2 years	In good health.....	
	9/28/16		15	41.0	154.0	88	43.3	+ 1	+	symmetrical, Soft, smooth,	0		In good health.....	No information
	1/13/17		16	42.5	155.8	87	44.5	+ 3	0	symmetrical .....	0		In good health.....	
24	6/ 2/15	♀	25	52.0	169.0	90	38.2	+ 3	+	Soft, smooth, symmetrical	0	3½ years	Well but easily fatigued.....	About the same
61	6/14/16	♀	31	64.0	155.4	67	36.6	0	..	Asymmetrical, irregular goiter, probably mul- tiple cysts	0	1 year	Symptoms of toxemia at onset; none now after course of roentgen ray	No information
70	9/16/16	♀	20	49.8	158.2	82	36.5	- 1	+	Soft, smooth, symmetrical	0	2 years	Slightly nervous; eyes somewhat prominent	Appears neurotic rather than thyr- oid
76	9/25/16	♀	43	68.0	167.5	87	33.3	- 7	++	Firm, smooth, asymmetrical	0	2 years	Marked psychoneurosis .....	No information
82	10/ 4/16	♀	30	67.0	172.0	77	39.7	+ 9	++	Soft, smooth, symmetrical	0	6 years	Slight toxemia in past, well now following course of roentgen ray	No information
85	10/12/16	♀	35	47.3	160.0	76	37.6	+ 3	+++	Soft, smooth, symmetrical	0	10 years	Well but easily fatigued.....	No information
90	10/18/16	♀	22	54.7	158.0	76	38.8	+ 5	++	Soft, smooth, symmetrical	+	6 months	Toxemia in past, clearing up on course of roentgen ray	No information
91	10/20/16	♀	34	57.5	163.0	106	42.6	+17	++	Soft, smooth, symmetrical	0	34 years?	Marked neurasthenia, nystagmus...	No information
92	10/21/16	♀	20	46.6	157.0	94	41.3	+12	++	Soft, smooth, symmetrical	0	2 years	Debility .....	No information
98	11/ 3/16	♀	47	60.0	157.5	79	38.2	+ 6	++	Soft, smooth, symmetrical	0	2 years	Nervous in past, clearing up on course of roentgen ray	Better; no evidence of Graves disease
132	1/18/17	♀	30	63.0	176.0	64	35.1	- 4	++	Soft, smooth, symmetrical	0	2 years	Some nervousness in past; none now	Goiter the same; no signs of toxemia
133	1/18/17	♀	24	45.5	158.0	83	36.5	- 1	+	Soft, smooth, symmetrical	0	24 years?	Somewhat nervous; history of in- creased sweating; slight tremor	No information
140	2/10/17	♀	22	63.0	163.5	87	40.1	+ 8	+	Soft, smooth, symmetrical	0	15 years	Occasionally nervous; slight tremor	Goiter the same; no signs of toxemia
145	2/20/17	♀	41	57.0	175.0	101	39.6	+10	..	Round, smooth mass in left lobe size of pigeon's egg; probably cyst	0	15 years	In good health.....	Goiter just as before; no signs of toxemia
150	3/ 4/17	♀	15	51.5	160.0	85	38.5	-10	..	Hard, round mass in left- mus size of a grape	0	15 years	Slight suggestion of myxedema....	No information

TABLE 3.—METABOLISM DATA. BORDERLINE CASES

No.	Date	Sex	Age	Weight, Kg.	Height, Cm.	Pulse	Calories per Square Meter and Hour	Peren- tile Vari- ation from Standard	Remarks	Patient's Condition in Spring of 1919
9	3/13/15	♀	51	58.2	169.0	133	47.2	+35	Tachycardia of unknown origin.....	No information
26	{ 6/22/15 4/ 9/19 7/ 8/15 1/20/17	♀	{ 33 37 30 31	{ 60.0 59.5 50.3 51.5	{ 158.0 151.0 151.0 158.8	{ 97 107 59 81	{ 44.9 55.5 42.6 44.6	{ +23 +52 +17 +22	Mitral disease plus suggestive symptoms..... Slight but definite signs of thyrotoxicosis..... Full thyroid; slightly suggestive symptoms..... Slight eye signs; no thyroid enlargement or toxic symptoms	Definitely Slightly thyrotoxic Not much evidence of Graves' disease; asthma her chief trouble No information
35	10/21/15	♀	34	43.0	158.8	99	36.0	-1	Tachycardia of unknown origin.....	No definite evidence of Graves' disease
46	12/14/15	♂	18	56.0	173.0	99	45.0	+10	Prolonged irradiation; ? of hypothyroidism.....	No evidence of throid disease
65	8/28/16	♀	46	67.0	165.0	87	31.3	-13	Very slight fullness of thyroid, eye signs and toxic symptoms	No information
73	9/20/16	♀	37	63.0	164.0	89	38.7	+6	Postoperative Graves'; slight recurrence of symptoms improved; slight tremor; slight nervousness; otherwise no evidence of thyrotoxicosis	Essentially normal
74	{ 9/21/16 4/ 7/19	♀	{ 36 39	{ 37.5 37.0	{ 155.5 155.5	{ 84 82	{ 34.9 36.5	-4 +1	Slight fullness of thyroid; very mild symptoms.....	Normal
75	4/22/16	♀	20	61.5	162.5	90	38.7	+5	Prolonged irradiation; atypical symptoms now.....	Seems to fall best in class of "effort syndrome"
78	{ 4/27/16 4/29/16 4/29/16	♀	{ 22 22 21	{ 55.4 55.4 38.9	{ 171.0 149.0 171.0	{ 89 72 113	{ 51.1 45.0 38.6	+29 +14 +4	Full thyroid; slight symptoms.....	In good health
80	10/ 3/16	♀	23	60.2	171.0	90	43.5	+10	Slight enlargement of thyroid, and somewhat atypical symptoms	No information
81	10/10/16	♀	24	49.2	161.3	88	43.5	+20	Slight fullness of thyroid; suggestive symptoms.....	Picture of very mild Graves' disease
84	{ 2/12/17 11/10/16	♀	{ 24 15	{ 49.3 41.0	{ 163.6 156.5	{ 86 126	{ 43.6 43.1	+18 0	Intrathoracic goiter .....	No evidence of Graves' disease; moderately neurotic
103	{ 11/11/16 2/ 8/17 11/21/16	♀	{ 53 53 50	{ 69.0 66.5 54.3	{ 161.8 169.5	{ 83 79 104	{ 40.1 37.9 54.1	+15 +8 +44	No eye signs or goiter but very suggestive symptoms	No information
112	11/21/16	♀	50	54.3	169.5	104	54.1	+44	Incipient phthisis .....	Subsequently developed true Graves' disease
115	11/24/16	♀	26	58.4	166.0	88	41.3	+12	Colloid goiter; ? hyperthyroidism.....	No information
116	11/25/16	♀	65	42.0	156.0	133	44.6	+31	Full thyroid and suggestive symptoms.....	In good health
118	12/ 1/16	♀	36	51.6	167.0	88	39.0	+7	Enlarged thyroid and atypical symptoms.....	No information
105	11/12/16	♀	43	55.5	157.0	99	43.9	+22	Chronic alcoholism with suggestive symptoms.....	No information
134	3/19/17	♀	36	69.0	170.0	103	43.3	+19	Enlarged thyroid; suggestive symptoms.....	No information
136	{ 1/29/17 4/12/19	♀	{ 32 32	{ 55.5 58.0	{ 156.0 156.0	{ 104 88	{ 46.9 45.9	+25 +26	Improved; five roentgen ray treatments; no evidence of hyperthyroidism now	Probably had mild attack of Graves' disease in interim
146	9/21/17	♀	34	60.3	171.0	89	36.8	+1	Enlarged thyroid; suggestive symptoms.....	No information
147	{ 2/22/17 9/26/17	♀	{ 51 51	{ 41.3 41.3	{ 152.0 152.0	{ 90 98	{ 54.3 53.8	+55 +54	Colloid goiter and suggestive symptoms.....	No information
149	9/24/17	♀	44	50.5	162.5	106	49.3	+37	Suggestive symptoms; no eye signs or goiter.....	Symptoms about as before
152	3/ 7/17	♀	39	70.5	179.0	90	51.4	+30	Suggestive symptoms .....	Developed true Graves' disease; better now
153	8/1 9/17	♀	93	55.0	172.0	93	43.9	+19	Full thyroid; no symptoms .....	Perfectly well
154	3/10/17	♀	58	58.8	159.0	94	40.0	+14	Postoperative Graves' disease.....	No information
155	3/10/17	♀	49	70.0	166.0	89	41.9	+9	Marked exophthalmos; no goiter or symptoms.....	Exophthalmos persists; no other signs of Graves' disease
157	3/13/17	♀	20	56.9	169.0	104	49.5	+34	Full thyroid; no symptoms.....	No information
159	3/15/17	♀	63	59.0	167.5	102	57.1	+56	Recurrent carcinoma of thyroid.....	No information
162	4/ 7/17	♀	53	46.5	162.5	89	38.8	+11	Tachycardia of unknown origin.....	No information
127	1/11/17	♀	31	55.0	178.0	105	38.3	+4	Neurasthenia .....	About the same

most part patients with goiters, but without clinical signs of thyrotoxicosis, have a normal metabolism, and that, furthermore, such cases do not subsequently become toxic. The metabolism determination, therefore, seems to be an excellent means of differentiating toxic and nontoxic goiters. Table 3 indicates that in cases with suggestive symptoms those patients with a normal metabolism do not subsequently develop exophthalmic goiter, while those with an elevation often-times do. In this class of cases, therefore, the metabolism determination appears to differentiate between true hyperthyroidism and simple neurasthenia, and makes possible a far earlier diagnosis of exophthalmic goiter than would the clinical picture alone.

*Exophthalmic Goiter.*—The data of our exophthalmic goiter series are presented in Tables 4, 5 and 6. It will be well to give short histories of these cases, fifty-five in number. The physical findings in each case at the time our first observation was made are indicated by plus marks, one meaning slight, two moderate, three marked. The statement as to the toxicity at the head of each history is based on the clinical impressions, not on the metabolism findings. For all dates the reader is referred to the several tables.

Table 4 shows the results obtained in fifteen cases in which the patients received essentially no treatment except with the roentgen ray, either alone or combined with rest. This table includes:

CASE 10.—Mrs. M. J. M. (E. M. 200812, X-Ray 306). Duration, six months. Very toxic. Eye signs + +. Tremor + +. Thyroid moderately enlarged, hard; loud bruit.

After ten roentgen-ray treatments she showed no improvement, objectively, in her metabolism, or in her pulse rate. She thought she felt better, but she gained no weight. She died (Oct. 3, 1917) sixteen months after her last metabolism determination, presumably of exophthalmic goiter.

CASE 12.—Mrs. T. W. (E. M. 200595, X-Ray 703). Duration eight years. Slightly toxic. Eye signs, none. Tremor +. Thyroid moderately enlarged, hard; faint bruit; definite myocarditis.

A somewhat atypical case of long standing goiter which, according to the history, had only recently become toxic; for some reason when first seen had been receiving a course of thyroid extract. She presented the picture of mild hyperthyroidism, but the metabolism was elevated 71 per cent. After cessation of thyroid and the administration of quinin hydrobromid, it dropped to 49 per cent., while her pulse dropped from 104 to 80. After six roentgen-ray treatments there was essentially no change in the metabolism and a slight rise in pulse and weight. She was seen this year and did not appear toxic, although the goiter persists. Myocardial insufficiency seemed the chief trouble. A metabolism determination was not obtained.

CASE 21.—Miss J. D. (E. M. 201753, X-Ray 519). Duration, two months. Moderately toxic. Eye signs +. Tremor + + +. Thyroid moderately enlarged; loud bruit.

After five roentgen ray treatments she showed a very striking improvement, fall in metabolism and pulse and gain in weight. She died December, 1917. The cause of death could not be learned.

CASE 25.—Mrs. A. L. (E. M. 202294, X-Ray 278). Duration, four months. Moderately toxic. Eye signs, none. Tremor +. Thyroid slightly enlarged, soft; bruit very loud. She showed a fall in metabolism and pulse rate and a gain in weight after four treatments, but no immediate further improvement after three additional treatments. When seen this year she did not appear to be toxic and her symptoms seemed referable to myocarditis. There was no longer any thyroid enlargement, and no eye sign or tremor.

CASE 33.—Mr. B. S. (E. M. 204683, X-Ray 591). Duration, two years. Moderately toxic. Eye signs +. Tremor + +. Thyroid moderately enlarged, soft; bruit + +.

He recovered completely after no other treatment than six roentgen-ray exposures, and he has remained well for over two years doing full work. His last metabolism figure was 14 per cent. below normal, but he presented no clinical signs of myxedema.

CASE 48.—Mrs. E. N. (E. M. 205776, X-Ray 693). Duration, four and one half years. Very toxic. Eye signs + + +. Tremor + +. Thyroid moderately and asymmetrically enlarged. Loud bruit.

After thirteen roentgen-ray treatments she has shown a marked improvement, fall in metabolism and pulse. When seen this year she showed slight exophthalmos, but no sign of intoxication. She had become very obese.

CASE 53.—Mr. R. S. (E. M. 206770, X-Ray 729). Duration, three weeks. Moderately toxic. Eye signs + + +. Tremor + + +. Thyroid slightly and symmetrically enlarged, soft. Loud bruit.

He showed essentially no change after seven treatments, but a year later, without further treatment, he showed a marked improvement, fall in metabolism and pulse rate, and gain in weight. He has not been seen this year, but writes that he was accepted for the U. S. Army, went overseas with his organization and has now been discharged and is working in a shipyard.

CASE 66.—Miss E. C. C. (O. P. D. 306686, X-Ray 888). Duration, two years. Moderately toxic. Eye sign +. Tremor +. Thyroid slightly and symmetrically enlarged, rather hard. Moderate bruit.

She had only roentgen-ray treatment. After eleven exposures she had recovered completely. When seen this year she presented no evidence of intoxication and had a normal metabolism. She was working to full capacity.

CASE 107.—Mrs. R. M. (O. P. D. 255857, roentgen ray 964). Duration, three years. Slightly toxic. Eye signs +. Tremor +. Thyroid slight; hard, enlargement of the right lobe. Slight bruit. This patient had had a hemithyroidectomy two years before our first observation, with recurrence of symptoms recently.

She grew distinctly worse after four roentgen-ray treatments. Her present condition has not been learned.

CASE 110.—Miss E. M. (E. M. 211726, X-Ray 1011). Duration, five months. Slightly toxic. Eye signs +. Tremors +. Thyroid slight, soft, symmetrical enlargement. Moderate bruit.

She showed no fall in metabolism on rest alone and then recovered after six roentgen-ray treatments. When seen this year she showed very slight tremor and slightest fullness of the thyroid. Her metabolism was just above normal and she was working to full capacity.

CASE 111.—Mrs. S. S. (E. M. 211757, X-Ray 1012). Duration, two months. Very toxic. Eye signs negative. Tremor + + +. Thyroid moderate soft, symmetrical enlargement. Loud bruit.

After thirteen roentgen-ray treatments she has had a marked fall in metabolism and pulse rate, and a good gain in weight. When seen this year she was clinically improved. She was still toxic, but all signs and symptoms were less marked. She was doing her own housework.

TABLE 4.—METABOLISM DATA. EXOPHTHALMIC GOITER. ROENTGEN-RAY SERIES

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Percent- tile Vari- ation from Stan- dard	Roent- gen Ray Treat- ments No.	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
							Subjec- tively	Objec- tively		
No. 10 Mrs. M. J. M. 50 years 157 Cm.	3/14/15	63.5	127	59.0	+68	0	.....	.....	A 2 days	On course of opium since last observation On quinin hydrobromid since last observation Doing considerable house work for year; appearance unchanged
	3/20/15	....	119	58.7	+68	0	Same	Same	A	
	4/2/15	57.2	108	53.1	+52	1	Improved	Worse	A	
	5/18/16	....	127	65.7	+88	9	Improved	Same	C	
No. 12 Mrs. T. W. 41 years 154.5 Cm.	3/26/15	40.0	104	61.5	+71	0	.....	.....	D	Had been taking thyroid extract; discontinued On quinin hydrobromid since last observation; dis- continued Goiter smaller
	4/17/15	....	80	53.7	+46	0	Same	Same	D	
	12/14/16	43.9	96	52.6	+46	6	Improved	Same	D	
No. 21 Miss J. D. 37 years 164 Cm.	5/19/15	45.0	77	54.9	+50	0	.....	.....	A 2 weeks	Goiter smaller; much less nervous Working for over a year
	6/8/15	....	81	55.8	+53	1	Improved	Improved	A	
	6/26/15	....	85	54.9	+50	2	Improved	Improved	A	
	1/31/17	63.2	67	41.3	+13	2	Almost well	Almost well	D	
No. 25 Mrs. A. L. 34 years 153 Cm.	6/8/15	50.5	117	63.8	+68	0	.....	.....	A 3 days	Feels and looks much better than last year
	12/12/16	56.6	106	58.7	+61	4	Improved	Improved	D	
	5/2/17	53.2	113	59.5	+63	3	Improved	Improved	D	
No. 33 Mr. B. S. 24 years 169.5 Cm.	10/12/15	50.0	103	70.3	+78	0	.....	.....	A 1 day	Better; tremor most troublesome symptom, inter- feres with work; barber practically well; tremor nearly gone Perfectly well; working Working since last observation
	6/5/16	52.7	96	59.6	+51	4	Improved	Improved	C	
	11/23/16	57.0	65	45.2	+14	2	Improved	Well	D	
	2/1/17	60.0	73	39.8	+1	0	Well	Well	D	
	5/5/19	59.0	56	34.1	-14	0	Well	Well	D	
No. 48 Mrs. E. N. 30 years 168 Cm.	1/1/16	52.0	137	66.3	+82	0	.....	.....	A 2 weeks	Less tremor; less exophthalmos Signs of thyrotoxicosis much less marked; some myo- cardial damage Leading normal life for 2 years
	1/21/16	53.5	123	58.8	+61	1	Improved	Improved	A	
	2/2/16	53.3	118	59.0	+62	0	Same	Same	A	
	6/9/16	60.0	102	58.9	+61	0	Same	Same	C	
	10/16/16	69.5	120	59.5	+63	0	Improved	Improved	D	
	1/8/17	68.0	96	56.1	+54	4	Same	Improved	D	
	4/26/17	74.3	98	46.0	+26	4	Improved	Improved	D	
	4/14/19	90.0	97	46.3	+27	3	Well	Well	D	
	5/13/19	87.0	88	45.8	+25	0	Well	Well	D	
	2/16/16	64.5	100	58.5	+48	0	.....	.....	A 2 days	
	5/17/16	61.0	98	62.1	+57	2	Same	Same	C	
No. 53 Mr. R. S. 21 years 171.5 Cm.	11/20/16	65.5	96	63.1	+60	5	Improved	Same	C	Eye signs less marked than a year ago; not objec- tively nervous now
	2/13/17	63.0	92	59.0	+49	0	Well	Same	C	
	12/12/17	66.0	70	44.6	+13	0	.....	.....	D	

No. 66 Miss E. C. O. 27 years 174.5 Cm.	8/29/16 12/ 2/16 2/24/17 4/ 7/17 4/12/19	48.2 49.6 50.0 49.0 49.0	118 118 104 104 80	52.6 49.2 41.8 47.3 34.6	+42 +33 +13 +28 - 6	0 4 2 1 4	..... Improved Improved Same Well	..... Improved Improved Same Well	D D D D D	Teebing school; almost no tremor Thyroid smaller; less bruit No eye signs; no tremor; no thyroid enlargement
No. 107 Mrs. R. M. 51 years 156 Cm.	11/16/16 1/27/17 4/ 5/17	45.0 45.5 49.0	81 106	49.3 42.5 53.8	+41 +21 +54	0 3 1	..... Well Worse	..... Well Worse	D D D	Leading normal life; appears and feels well Reurrence of symptoms following overwork
No. 110 Miss E. M. 39 years 157.5 Cm.	11/19/16 11/24/16 12/ 3/16 12/18/16 1/30/17 3/ 8/17 4/ 9/17 5/ 7/19	56.8 56.6 54.7 56.8 61.0 64.7 65.5 66.5	96 112 108 109 105 91 84 78	49.0 51.7 49.1 51.7 48.9 42.8 36.3 41.3	+34 +42 +35 +42 +34 +17 - 1 +15	0 0 1 0 2 2 2 0	..... Improved Improved Same Improved Improved Well	..... Improved Improved Same Improved Improved Well	A 4 days A A A C C D D	Quinin hydrobromid for last ten days  Thinks she is much better; still looks toxic Appears less toxic Been back at work for six weeks
No. 111 Mrs. S. S. 55 years 151.2 Cm.	11/19/16 11/26/16 12/ 5/16 1/10/17 3/ 8/17 4/15/19	39.0 38.5 114 40.0 41.0 48.5	131 129 114 140 141 100	65.4 64.1 55.0 65.6 64.7 44.0	+87 +83 +57 +85 +87 +26	0 0 1 1 2 9	..... Same Improved Improved Same Improved	..... Same Improved Improved Same Improved	A 2 days A A C C C D	Extreme nervousness  Less nervous  Very slight tremor; thyroid barely perceptible
No. 113 Mrs. B. M. T. 23 years 155.8 Cm.	11/22/16 1/25/17 3/12/17 4/29/17	58.0 55.0 54.5 55.2	153 116 110 133	65.6 54.6 51.6 54.3	+77 +48 +39 +47	0 2 2 0	..... Same Same Same	..... Improved Improved Same	D D A 1 week A 1 week	Acute infection for last two weeks Had diphtheria between this and preceding observation
No. 120 Mrs. I. K. 45 years 160 Cm.	12/ 7/16 12/22/16 1/31/17 3/29/17	53.6 49.5 50.5 53.5	128 130 112 114	60.2 61.6 56.2 53.4	+67 +71 +56 +48	0 0 2 2	..... Same Improved Improved	..... Same Same Improved	D C D D D	Exophthalmos increasing Seems less toxic but eye signs are increasing and thyroid enlarging
No. 123 Mrs. C. Mv. 29 years 152.5 Cm.	12/14/16 12/20/16 1/ 9/17 1/13/17 1/21/17 2/ 1/17 3/ 3/17 4/24/17 4/26/18 5/ 7/19	48.0 49.0 42.3 43.0 43.6 43.9 43.5 51.0 56.0 55.0	157 133 112 118 127 122 128 125 122 111	70.0 64.2 49.7 51.9 57.5 57.5 58.6 64.4 63.9 60.5 50.6	+39 +74 +34 +40 +55 +58 +74 +73 +66 +39	0 1 0 0 0 1 0 3 1 0	..... Same Improved Improved Worse	..... Same Improved Improved Worse Same Improved Same	C A 1 day A A A A C D D	Much better; looking after husband and two children
No. 135 Mrs. V. M. D. 39 years 164.5 Cm.	1/28/17 2/ 7/17 2/15/17 3/ 9/17 4/ 5/17 1/30/18 5/10/19	53.2 53.7 53.9 57.5 58.1 56.0 65.5	122 106 108 119 108 116 104	50.6 44.4 46.9 53.5 46.1 45.1 37.5	+39 +22 +28 +47 +27 +25 + 4	0 0 0 0 1 6 0	..... Improved Improved Worse Well	..... Improved Improved Same Same Well	A 11 days A A C C D	Quinin hydrobromid for six months Less exophthalmos Doing light housework Has had a healthy child since last observation

CASE 113.—Mrs. B. M. T. (E. M. 213651, X-Ray 1015). Duration, three years. Moderately toxic. Eye signs +. Tremor + +. Thyroid moderate, soft, symmetrical enlargement. Faint bruit.

She improved somewhat after four roentgen-ray treatments but died later, the date and cause of death being unknown to us.

CASE 120.—Mrs. I. K. (O. P. D. 315898, X-Ray 1029). Duration, one year. Moderately toxic. Eye signs + + +. Tremor + + +. No visible enlargement of thyroid.

She showed some improvement after four roentgen-ray treatments. Subsequently she has remained in fairly good health, but both eyes have had to be enucleated because of extreme exophthalmos.

CASE 123.—Mrs. C. M. (E. M. 212328, X-Ray 1020). Duration, eight years. Very toxic. Eye signs + + +. Tremor + + +. Thyroid marked, soft, symmetrical enlargement. Loud bruit.

After six roentgen-ray treatments she showed a definite improvement; fall in metabolism and pulse and gain in weight. When seen this year she was clinically improved. The exophthalmos persists. Slight tremor was present. The goiter was smaller. She was still somewhat toxic but was working to usual capacity.

CASE 135.—Mrs. V. M. D. (W. M. 212958, X-Ray 872). Duration, one year. Slightly toxic. Eye signs + + +. Tremor +. Thyroid slight, soft symmetrical enlargement. Faint bruit.

She recovered after seven treatments. When seen this year, except for slight exophthalmos and a persistent tachycardia she showed no signs or symptoms of exophthalmic goiter. Her metabolism was normal, and she was caring for her family and nursing her baby.

In Table 5 are collected the data obtained in sixteen cases before and after partial thyroidectomy.

CASE 3.—Mrs. L. S. (W. M. and W. S. 197641). Duration, four years. Very toxic. Eye signs + +. Tremor + +. Thyroid moderate, soft symmetrical enlargement. Loud bruit.

One year and one half after lobectomy she showed a fall in metabolism and a gain in weight. No change occurred in her pulse rate. Her condition this year could not be learned.

CASE 16.—Mr. S. T. (W. M. and W. S. 201372). Duration, one year. Moderately toxic. Eye signs + +. Tremor + + +. Thyroid, moderate, soft symmetrical enlargement.

Two years after operation he showed a higher metabolism than he did before. Essentially, no change in pulse rate and a slight gain in weight. His condition this year could not be learned.

CASE 51.—Mr. W. W. H. Duration, eight months. Slightly toxic. Eye signs +. Tremor +. Thyroid, slight fullness; faint bruit. He gave a history of no improvement after six roentgen-ray treatments. After lobectomy at the Mayo clinic he gained weight, had a normal metabolism and a slower pulse. Later he had a slight return of toxemia. He has not been seen this year, but writes that he is quite well.

CASE 71.—Mrs. H. R. (E. M. and W. S. 210587, X-Ray 794). Duration eighteen months. Moderately toxic. Eye signs +. Tremor +. Thyroid, moderate, soft symmetrical enlargement.

She gave a history of no improvement after eight roentgen-ray treatments. This was before coming under our observation. She showed a striking fall in metabolism and pulse rate immediately after operation and later a rise. This year her metabolism is still 22 per cent. above normal, but she has gained weight, has no tachycardia and appears to be well. There is still slight exophthalmos. She is following her usual occupation.

CASE 83.—Mr. W. H. (W. M. and W. S. 210852). Duration, one year. Very toxic. Eye signs + + +. Tremor +. Thyroid, moderately enlarged. Faint bruit.

When first seen he was still toxic in spite of a ligation done at the Mayo Clinic. He showed a striking improvement after lobectomy and had a normal metabolism and pulse rate one month after operation. His condition this year was not learned.

CASE 88.—Miss C. P. (E. M. and W. S. 211054, X-Ray 879). Duration, one year. Very toxic. Eye signs + + +. Tremor + +. Marked, soft symmetrical enlargement of thyroid. Loud bruit.

She gave a history of no improvement after four roentgen-ray treatments, but showed a marked improvement after ligation and then grew worse again after lobectomy. This year, however, she is looking and feeling well, and her metabolism is only + 15 per cent. She has been working for two years; a slight exophthalmos remains.

CASE 99.—Miss M. T. P. (W. M. and W. S. 211454, X-Ray 1094). Duration, eleven years. Very toxic. Eye signs + + +. Tremor + + +. Thyroid, marked asymmetric enlargement. Loud bruit.

This patient also reported no improvement after eight roentgen-ray treatments. She showed an increase in toxemia following lobectomy, but later a gradual improvement under roentgen-ray treatment. When seen this year she still had a slight exophthalmos, slight fullness of the left lobe of the thyroid, with bruit, but other signs and symptoms of thyrotoxicosis were practically absent. Her metabolism was decreased and she had been working to full capacity for one year and one half.

CASE 106.—Mrs. N. M. (E. M. and W. S. 211553). Duration, two years. Slightly toxic. Eye signs, none. Tremor +. Thyroid, moderate, hard, asymmetrical enlargement. No bruit.

She apparently became entirely normal within four months after lobectomy. This year she was clinically well, but her metabolism was + 24 per cent.

CASE 117.—Miss V. R. (W. M. and W. S. 211801). Duration, two years. Slightly toxic. Eye signs +. Tremor + +. Thyroid, slight soft symmetrical enlargement. Faint bruit.

After operation she showed an immediate decrease followed by an increase in toxemia. However, she writes this year that she is in excellent health. She has been married and is doing her own housework.

CASE 125.—Miss M. D. (E. M. and W. S. 212305). Duration, one and one half years. Very toxic. Eye signs, +. Tremors, + + +. Thyroid, moderate, hard, symmetrical enlargement. Loud bruit.

She had had a ligation before coming under our observation. She showed a marked fall in pulse rate and metabolism on rest in bed, and a continued gradual improvement after a ligation and lobectomy. When seen this year she had a slight exophthalmos and a hard mass in the isthmus of the thyroid, the size of a pigeon's egg; no bruit. There was no evidence of thyrotoxicosis. Metabolism was decreased and she had been working for two years as a domestic.

CASE 126.—Mrs. M. L. (W. M. and W. S. 212598). Duration, eighteen months. Slightly toxic. Eye signs, +. Tremor, +. Thyroid, slight soft symmetrical enlargement. Faint bruit.

She had had nine roentgen-ray treatments before coming under our observation. She showed a return of the metabolism to normal, a normal pulse rate and a gain in weight after lobectomy. She died subsequently. We have been unable to learn the date and cause of death.

CASE 129.—Mr. W. E. R. (W. M. and W. S. 212711). Duration, one year. Slightly toxic. Eye signs, none. Tremor + +. Thyroid, slight fullness. No bruit.

TABLE 5.—METABOLISM DATA, EXOPHTHALMIC GOITER, SURGICAL SERIES

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Per- cent- ile Varia- tion from Stan- dard	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
						Subjec- tively	Objec- tively		
No. 3 Mrs. L. S. 35 years 157 Cm.	10/ 8/14	42.0	104	65.6	+80	.....	.....	A 3 weeks	Three roentgen ray treatments before coming under observation
	10/10/14	42.0	102	63.1	+73	Same	Same	A	One roentgen ray treatment
	11/ 6/14	39.2	104	59.0	+62	Improved	Improved	A	Lobectomy Oct. 16, 1914
	6/ 6/16	53.0	108	54.5	+49	Improved	Improved	D	Much better; all signs and symptoms greatly diminished; working
No. 16 Mr. S. T. 33 years 168 Cm.	4/19/15	62.7	100	51.4	+30	.....	.....	A 1 day	
	3/31/17	67.0	96	57.1	+45	Same	Improved	D	Lobectomy April 20, 1915
No. 51 Mr. W. W. H. 33 years 174.5 Cm.	2/ 8/16	54.6	108	55.2	+40	.....	.....	C	Six roentgen ray treatments before coming under observation
	6/30/16	58.0	80	40.4	+2	Improved	Well	C	Lobectomy May 19, 1916, at Mayo Clinic
	12/22/16	61.5	96	47.0	+19	Worse	Worse	D	Back at work in banking business
	9/19/16	68.0	113	49.6	+36	.....	.....	A 1 day	Had eight roentgen ray treatments before coming under observation, without improvement
No. 71 Mrs. H. R. 37 years 166.5 Cm.	9/23/16	67.6	101	51.1	+40	Improved	Improved	A	Lobectomy Sept. 25, 1916
	10/ 2/16	65.9	88	42.1	+15	Improved	Improved	A	
	10/31/16	69.5	122	49.8	+36	Improved	Improved	C	
	11/14/16	70.5	113	49.4	+35	Improved	Same	D	
	12/12/16	70.9	101	46.1	+26	Worse	Same	D	
	2/ 3/17	72.5	104	45.5	+25	Same	Improved	D	
	3/11/17	73.5	93	43.8	+20	Well	Improved	D	
	4/ 1/19	77.5	88	44.8	+23	Well	Well	D	
No. 83 Mr. W. H. 22 years 160 Cm.	4/29/19	76.0	80	44.5	+22	Well	Well	D	
	10/ 5/16	49.9	127	61.7	+56	.....	.....	A 3 days	Ligation at Mayo Clinic July, 1916, superior arteries
	10/ 9/16	52.0	96	53.7	+36	.....	.....	A	
	10/27/16	45.5	97	51.5	+30	Improved	Improved	A	Lobectomy Oct. 16, 1916
	11/18/16	43.6	81	42.8	+ 8	Improved	Improved	C	

No. 88 Miss C. P. 36 years 161 Cm.	10/14/16	54.7	144	64.1	+73	..... Improved Improved Improved Improved Improved	..... Same Improved Improved Improved Improved	A 3 days A A A A A C D D	Had four roentgen ray treatments before coming under observation, without improvement  Ligation Nov. 2, 1916 Lobectomy Nov. 17, 1916 All signs and symptoms less marked  Exophthalmos nearly gone; no tremor; no thyroid palpable
	10/18/16	54.7	141	57.1	+54	.....	.....		
	10/26/16	51.8	143	56.1	+52	.....	.....		
	11/11/16	51.0	124	44.3	+20	.....	.....		
	11/29/16	52.3	129	47.3	+28	.....	.....		
No. 99 Miss M. T. P. 36 years 170.6 Cm.	12/11/16	51.1	127	47.8	+29	.....	.....		Had eight roentgen ray treatments before coming under observation, without improvement Quinin hydrobromid since last note  Lobectomy Nov. 23, 1916  Four roentgen ray treatments One roentgen ray treatment
	1/11/17	52.5	142	55.3	+49	.....	.....		
	3/30/17	55.0	116	56.9	+54	.....	.....		
	11/22/17	54.5	Lost	46.7	+26	.....	Well		
	4/27/19	48.5	90	42.5	+15	.....	Well		
No. 106 Mrs. N. M. 41 years 158.5 Cm.	11/ 3/16	59.5	112	62.7	+72	.....	.....	A 1 day	Ligation at St. Lukes Hospital, New Bedford, May, 1916 One roentgen ray treatment since last observation  Ligation Jan. 19, 1917 Lobectomy Jan. 30, 1917  Working for nearly two years
	11/ 7/16	55.8	110	57.5	+53	.....	.....		
	11/15/16	54.5	89	51.7	+42	.....	.....		
	12/16/16	49.0	103	50.9	+39	.....	.....		
	2/19/17	56.0	119	58.5	+60	.....	.....		
No. 117 Miss V. R. 22 years 168.2 Cm.	2/28/17	59.1	101	55.8	+53	.....	.....		Ligation Jan. 19, 1917 Lobectomy Jan. 30, 1917  Working for nearly two years
	4/18/17	61.0	103	53.4	+46	.....	.....		
	9/13/17	65.0	96	45.3	+24	.....	.....		
	3/27/19	59.0	76	45.7	+25	.....	.....		
	11/14/16	37.4	112	53.9	+50	.....	.....	A 1 week	
No. 125 Miss M. D. 27 years 166.3 Cm.	11/19/16	37.2	107	54.0	+50	.....	.....		Ligation at St. Lukes Hospital, New Bedford, May, 1916 One roentgen ray treatment since last observation  Ligation Jan. 19, 1917 Lobectomy Jan. 30, 1917  Working for nearly two years
	12/10/16	38.0	82	38.4	+ 7	.....	.....		
	2/26/17	42.5	77	42.2	+17	.....	.....		
	3/30/17	41.2	80	37.9	+ 5	.....	.....		
	8/ 5/19	48.0	74	44.7	+24	.....	.....		
No. 117 Miss V. R. 22 years 168.2 Cm.	11/26/16	46.6	114	53.5	+45	.....	.....	A 6 days	Ligation at St. Lukes Hospital, New Bedford, May, 1916 One roentgen ray treatment since last observation  Ligation Jan. 19, 1917 Lobectomy Jan. 30, 1917  Working for nearly two years
	12/ 2/16	45.9	110	47.2	+28	.....	.....		
	12/15/16	46.8	100	46.3	+25	.....	.....		
	12/27/16	49.6	108	51.3	+39	.....	.....		
	1/ 2/17	50.3	119	52.1	+41	.....	.....		
No. 125 Miss M. D. 27 years 166.3 Cm.	1/15/17	49.6	103	41.9	+13	.....	.....		Ligation at St. Lukes Hospital, New Bedford, May, 1916 One roentgen ray treatment since last observation  Ligation Jan. 19, 1917 Lobectomy Jan. 30, 1917  Working for nearly two years
	1/21/17	49.5	100	44.2	+19	.....	.....		
	1/30/17	50.7	99	44.5	+20	.....	.....		
	2/20/17	52.5	106	46.9	+27	.....	.....		
	3/25/17	51.0	102	48.6	+31	.....	.....		
No. 125 Miss M. D. 27 years 166.3 Cm.	12/18/16	53.2	133	70.6	+91	.....	.....	A 1 day	Ligation at St. Lukes Hospital, New Bedford, May, 1916 One roentgen ray treatment since last observation  Ligation Jan. 19, 1917 Lobectomy Jan. 30, 1917  Working for nearly two years
	12/26/16	53.0	99	59.4	+61	.....	.....		
	1/11/17	53.0	108	61.1	+65	.....	.....		
	1/19/17	50.5	91	55.7	+50	.....	.....		
	1/26/17	51.4	102	51.6	+39	.....	.....		
No. 125 Miss M. D. 27 years 166.3 Cm.	2/10/17	52.7	96	49.8	+35	.....	.....		Ligation at St. Lukes Hospital, New Bedford, May, 1916 One roentgen ray treatment since last observation  Ligation Jan. 19, 1917 Lobectomy Jan. 30, 1917  Working for nearly two years
	2/19/17	52.7	85	49.7	+34	.....	.....		
	3/28/17	59.0	79	46.9	+27	.....	.....		
	4/26/19	59.0	78	45.5	+23	.....	.....		
						.....	.....		

TABLE 5.—METABOLISM DATA. EXOPHTHALMIC GOITER. SURGICAL SERIES—Continued

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Peren- tile Vari- ation from Stand- ard	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
						Subjec- tively	Objec- tively		
No. 126 Mrs. M. L. 34 years 160 Cm.	1/ 7/17	49.3	122	53.5	+47	.....	.....	A 2 days	Had nine roentgen ray treatments before coming under observation Lobectomy Jan. 23, 1917
	1/20/17	50.3	105	52.6	+44	.....	.....	A	
	2/ 4/17	49.9	96	41.6	+14	Improved	Improved	A	
	2/11/17	49.3	105	43.4	+19	Improved	Improved	A	
	3/27/17 10/29/17	51.0 56.5	100 76	43.8 37.4	+20 + 2	Almost well	Almost well	O	
No. 129 Mr. W. E. R. 39 years 169.5 Cm.	1/14/17 5/ 7/19	47.7 52.5	145 96	58.9 39.8	+49 + 3	..... Well	..... Well	A 3 days D	Lobectomy Jan. 20, 1917, at private hospital
No. 137 Mr. E. T. B. 35 years 166.2 Cm.	2/ 3/17	53.0	112	67.5	+71	.....	.....	A 1 day	Had an acute throat infection since last note and developed auricular fibrillation Lobectomy March 5, 1917 Three roentgen ray treatments, spring of 1917
	2/16/17	55.0	119	63.5	+61	.....	.....	A	
	2/25/17	50.9	96	66.9	+69	Improved	Worse	A	
	3/ 2/17	51.6	102	61.6	+56	Improved	Improved	A	
	3/14/17 4/ 7/17 3/29/19	49.5 58.2 68.0	87 121 64	52.8 65.9 40.9	+34 +67 + 4	Improved Improved Well	Improved Improved Well	A A O D	
No. 143 Miss M. E. H. 36 years 156 Cm.	2/15/17	54.1	104	46.3	+27	.....	.....	A 3 days	Had seven roentgen ray treatments before coming under observation Lobectomy Feb. 24, 1917 Lobectomy June 30, 1917
	2/18/17	54.1	105	48.1	+32	.....	.....	A	
	3/ 4/17	53.0	107	43.3	+19	.....	.....	A	
	3/15/17	55.0	100	41.3	+13	.....	.....	A	
	4/20/17 4/ 9/19	53.6 54.5	92 64	46.6 32.3	+28 -11	Improved Well	Improved Well	C D	
No. 148 Miss B. H. 26 years 161 Cm.	2/23/17 6/25/17 5/ 1/19	47.0 46.0 56.5	110 94 60	56.2 54.1 40.9	+52 +46 +10	..... Well	..... Well	D A D	One roentgen treatment Lobectomy June 28, 1917
No. 151 Mrs. M. E. T. 46 years 158 Cm.	3/ 6/17	52.2	117	64.6	+79	.....	.....	A 1 day	Lobectomy March 27, 1917
	3/13/17	52.3	111	59.1	+64	.....	.....	A	
	3/19/17	51.4	102	56.6	+57	.....	.....	A	
	4/ 1/17	49.0	100	48.5	+35	.....	.....	A	
	5/ 9/19	49.0	117	50.3	+40	Improved	Improved	D	

Two years after lobectomy he had a normal metabolism and clinically was well. He was working to full capacity.

CASE 137.—Mr. E. T. B. (E. M. and W. S. 213101). Duration, six years. Moderately toxic. Eye signs +. Tremor + +. Thyroid, moderate soft, symmetrical enlargement. Faint bruit.

He showed little consistent improvement immediately after lobectomy. When seen two years later, he was well, but he had had three roentgen-ray treatments in that time. Slight exophthalmos persisted, but his metabolism was normal and he had been working for nearly two years.

CASE 143.—Miss M. E. H. (W. M. and W. S. 213273). Duration, ten months. Slightly toxic. Eye signs, none. Tremor + +. Thyroid, moderate, soft, symmetrical enlargement. Moderate bruit.

She had had seven roentgen-ray treatments before coming under our observation. She apparently was cured by two successive lobectomies. When seen this year she had no signs or symptoms of exophthalmic goiter. She had a normal metabolism, and had been working for more than one year.

CASE 148.—Miss B. H. (E. M. and W. S. 215081). Duration, two months. Very toxic. Eye signs +. Tremor +. Thyroid moderate, soft symmetrical enlargement. Faint bruit.

When seen this year, two years after operation, she had no signs or symptoms of exophthalmic goiter, except a slight exophthalmos. She had a normal metabolism, and had been working one year.

CASE 151.—Mrs. M. E. T. (W. M. and W. S. 213639). Duration, eight months. Moderately toxic. Eye signs +. Tremor + +. Thyroid, moderate, soft, symmetrical enlargement. Loud bruit.

When seen two years after lobectomy she still had an elevated metabolism and signs and symptoms of a slight thyrotoxicosis. She was doing light housework.

In Table 6 are collected a somewhat miscellaneous group, some in which the series of observations is incomplete, and some that were followed both during the roentgen-ray and the surgical treatments.

CASE 18.—Miss M. A. W. (E. M. 201409). Duration, six years. Slightly toxic. Eye signs +. Tremor, none. Slight thyroid enlargement.

She gave a history of having had a more severe exophthalmic goiter in the past, from which she had recovered. She improved rapidly on a short rest and quinin hydrobromid. She has remained well. She is working at her profession of nursing.

CASE 22.—Miss H. Duration, seven years. Moderately toxic. Eye signs + +. Tremor +. Thyroid, right lobe enlarged. Bruit present.

One observation only was made on this patient. She had a thyrotoxicosis recurring after a lobectomy done seven years before. She also showed an elevation of 43 per cent. in the basal metabolism. Her present condition is not known.

CASE 23.—Mrs. F. G. (E. M. and W. S. 201801, X-Ray 511). Duration, eight years. Very toxic. Eye signs + + +. Tremor + +. Thyroid, marked, hard enlargement. Loud bruit.

She died two days after ligation of the right superior thyroid vessels. The vessels on the left side had been ligated eleven days before.

CASE 32.—Mrs. E. J. S. (E. M. 204549). Duration, three years. Slightly toxic. Eye signs +. Tremor +. Thyroid, slightly and asymmetrically enlarged. No bruit.

This patient appeared clinically to be only slightly toxic, but she had a very high metabolism. When seen five and one half months later, having followed

TABLE 6.—METABOLISM DATA. EXOPHTHALMIC GOITER. MISCELLANEOUS

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Percen- tile Varia- tion from Stand- ard	Roent- gen Ray Treat- ment No.	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
							Subjec- tively	Objec- tively		
No. 18 Miss M. A. W. 31 years 164 Cm.	4/22/15	....	71	39.9	+9	0	.....	.....	A 1 week C D	On quinin hydrobromid
	10/23/16	48.0	86	41.5	+14	0	.....	.....		
	4/ 2/17	49.5	90	39.4	+8	0	.....	.....		
No. 22 Miss H. 35 years	5/23/15	65.5	105	52.1	+43	0	.....	.....	D	Lobectomy in 1908
	5/24/15	33.7	121	67.0	+81	1	.....	.....		
No. 32 Mrs. E. J. S. 38 years 163.5 Cm.	10/ 7/15	53.0	111	63.1	+73	0	.....	.....	A 5 days D	Goiter smaller
	3/28/17	55.0	120	68.4	+87	1	.....	.....		
	11/ 9/15	55.8	103	47.4	+23	0	.....	.....		
No. 52 Miss C. M. 22 years 170 Cm.	2/10/16	50.0	130	65.3	+76	0	.....	.....	A 6 days	Ligations, November and December, 1913; lobectomy March 2, 1916
	6/ 5/16	47.5	132	49.1	+36	0	.....	.....		
No. 62 Mrs. M. A. H. 40 years 155.3 Cm.	6/16/16	61.0	117	49.1	+36	4	.....	.....	C C C D	
	11/23/16	61.5	112	48.0	+33	5	.....	.....		
	3/29/17	60.0	106	47.7	+32	2	.....	.....		
	8/ 7/19	57.0	94	48.6	+35	0	.....	.....		

No. 68 Mrs. J. B. 35 years 159.2 Cm.	9/12/16 12/13/16 2/17/17 2/26/17 4/ 8/19	50.5 53.0 54.5 52.4 49.5	88 90 81 80 82	50.6 46.1 49.9 47.7 49.9	+39 +26 +37 +31 +37	9 2 3 0 8	..... Improved Worse Improved Improved	..... Improved Worse Improved Improved	D D A Same D
No. 72 Miss E. P. 18 years 161 Cm.	9/19/16 11/28/16	51.1 53.5	111 106	49.4 49.5	+30 +30	5 0	..... Improved	..... Improved	D D
No. 77 Mrs. S. I. R. 29 years 154.5 Cm.	9/26/16 10/ 7/16 10/21/16	53.4 50.0 49.1	151 133 124	54.6 54.5 58.5	+48 +47 +53	0 0 0	..... Same Improved	..... Same Improved	A 3 days A A
No. 89 Miss M. S. 23 years 162.5 Cm.	10/14/16 12/ 4/16 2/ 9/17 3/26/17	61.0 64.0 63.0 61.0	112 101 110 103	57.1 50.1 54.0 54.1	+54 +35 +46 +46	5 2 3 3	..... Improved Same Same	..... Same Improved Same	D D D D
No. 93 Mrs. A. B. 33 years 163 Cm.	10/27/16 1/ 7/17 1/22/17 2/13/17 2/24/17 3/ 3/17 3/28/17 2/ 4/18 4/ 1/19	55.2 51.9 53.5 53.7 55.5 57.2 58.0 59.0 59.0	131 133 129 125 103 99 102 93 83	51.0 49.9 50.3 49.8 38.4 38.4 38.1 36.6 33.7	+40 +37 +38 +37 +5 +7 +4 +4 - 8	0 2 1 1 0 0 0 0 0	..... Same Same Same Well Well Weak Improved	..... Same Same Same Improved Improved Same Well	C A 6 days A A A A A D D
No. 100 Miss F. McH. 14 years 147 Cm.	11/ 4/16 11/ 7/16	51.1 51.5	149 140	50.6 50.2	+41 +39	15 0	..... Same	..... Same	A 3 days A
No. 114 Miss O. S. 41 years 164.8 Cm.	11/23/16 1/10/17 5/ 8/17 7/ 2/19	55.0 65.5 63.0 60.5	107 76 73 68	53.0 34.9 33.0 34.5	+47 - 2 + 6 - 4	1 2 1 0	..... Improved Well Well	..... Well Well Well	O D D D
No. 121 Miss M. M. 21 years 152.5 Cm.	12/ 9/16 12/16/16 12/23/16 1/ 6/17 1/12/17 1/22/17 1/31/17 2/12/17 3/ 5/17 4/13/17 4/29/17 4/10/19	59.5 57.0 56.3 55.0 55.0 52.3 52.3 52.3 53.2 58.0 58.7 60.5	196 137 117 116 102 108 122 117 141 114 111 59	80.5 77.4 67.9 67.9 63.5 66.7 64.2 74.2 75.1 68.2 42.7 41.1	+118 +109 +84 +84 +72 +78 +74 +74 +103 +79 +58 +15 +11	0 0 0 1 1 0 0 0 1 1 1 0 3	..... Improved Improved Improved Same Same Improved Improved Same Same Improved Well	..... Improved Improved Improved Same Same Improved Same Same Same Improved Well	D A 1 day A A A A A A A B B A 2 days A D

Lobectomy Nov. 3, 1916

Working in shoe factory right along; has done so ever since onset

Just recovered from acute tonsillitis

Lobectomy Feb. 14, 1917  
Doing housework

Lobectomy April 16, 1917

TABLE 6.—METABOLISM DATA. EXOPHTHALMIC GOITER. MISCELLANEOUS—(Continued)

Number Age Height, Cm.	Date	Weight, Kg.	Pulse	Calories per Square Meter and Hour	Per- cent- tile Vari- ation from Stan- dard	Roent- gen Ray Treat- ments No.	Progress Judged Clinically		Activity: A. Complete Rest in Ward B. Complete Rest Outside C. Partial Rest D. Usual Life	Remarks
							Subec- tively	Objec- tively		
No. 130 Miss K. L. 17 years 167.7 Cm.	1/16/17	50.5	125	58.5	+46	0	.....	.....	A 1 day	
	1/17/17	50.2	120	54.1	+35	0	.....	.....	A	
	1/22/17	50.3	112	52.0	+30	0	Improved	Improved	A	
	1/30/17	49.5	103	52.5	+31	0	Same	Same	A	
	2/ 8/17	50.0	109	50.4	+26	0	Improved	Same	A	
	2/14/17	51.0	107	48.8	+22	0	.....	.....	A	
No. 131 Mrs. S. J. G. 33 years 178 Cm.	4/28/17	56.0	99	51.3	+28	0	Improved	Same	C	Lobectomy Feb. 24, 1917, at Melrose Hospital
	1/16/17	59.0	99	51.9	+42	0	.....	.....	A 3 days	
	1/22/17	59.5	81	48.6	+43	0	Improved	Improved	A	
	2/ 4/17	57.5	97	47.7	+31	0	Improved	Improved	A	
	3/22/17	55.3	96	48.1	+32	1	Same	Same	A	Just been through a bronchopneumonia and after that an acute frontal sinusitis. Never has had any consistent treatment
	4/26/19	61.5	77	44.5	+22	0	Improved	Well	D	Quinin hydrobromid for one week
No. 133 Mr. C. J. 38 years 168 Cm.	2/ 5/17	64.5	104	53.7	+36	0	.....	.....	D	
	2/19/17	67.5	102	55.8	+41	0	Same	Same	D	
	4/ 8/17	67.7	101	56.3	+43	0	Improved	Improved	D	
No. 139 Mrs. R. K. 23 years 161.5 Cm.	2/ 6/17	58.0	108	55.6	+50	1	.....	.....	D	
	4/12/17	55.0	107	54.6	+48	2	Improved	Same	D	
No. 144 Mrs. H. 37 years 163.7 Cm.	2/17/17	74.3	113	53.8	+47	0	.....	.....	A 3 days	Lobectomy July, 1914, Peter B. Brigham Hospital
	3/ 7/17	76.0	82	46.4	+27	0	.....	.....	A	
No. 156 Theodore D. 11 years 141.5 Cm.	3/12/17	28.8	124	65.6	+29	0	.....	.....	A 3 days	
	8/ 2/19	39.0	102	52.7	+15	4	Improved	Improved	D	
No. 160 Mrs. K. 57 years 170 Cm.	3/26/17	57.8	119	62.3	+78	0	.....	.....	A 2 days	Lobectomy April 13, 1917
	4/10/17	47.5	130	69.5	+99	1	Worse	Worse	A	
No. 161 Mrs. C. M. 26 years 165 Cm.	3/22/17	46.4	126	68.1	+84	0	.....	.....	A 12 days	Lobectomy Oct. 10, 1917
	4/ 6/17	45.5	128	61.6	+67	0	Same	Same	A	
	10/ 8/17	61.0	118	61.1	+65	0	.....	.....	A	

no treatment in the interim, she appeared and felt better, but had a still higher metabolism and pulse rate, and she had lost weight. Her present condition could not be learned.

CASE 40.—Mrs. D. K. N. (W. M. 205075). Duration, eighteen months. Moderately toxic. Eye signs +. Tremor +. Thyroid, slight fullness.

This patient was observed only once and has never been located since.

CASE 52.—Miss C. M. (E. M. 192096, W. S. 194108). Duration, three years. Very toxic. Eye signs + + +. Tremor + +. Thyroid, moderate, soft, symmetrical enlargement. Faint bruit.

She had had two ligations done two years before our observation. She died of acute pericarditis eleven days after lobectomy.

CASE 59.—Miss A. M. B. (W. S. 208734). Duration, eighteen years. Moderately toxic. Eye signs +. Tremor +. Thyroid, slight fullness. Slight bruit.

This patient was observed only once. We have not been able to locate her since.

CASE 62.—Mrs. M. A. H. (O. P. D. 289505, X-Ray 706). Duration, four and one half years. Slightly toxic. Eye signs + +. Tremor + + +. Thyroid, slight symmetrical enlargement.

She had had four roentgen-ray treatments before we started our observations. When seen this year she had had seven more. She was clinically better but her metabolism was unchanged. There still was slight exophthalmos. She had been working for two years.

CASE 68.—Mrs. J. B. (E. M. 213374, X-Ray 524). Duration, seven years. Moderately toxic. Eye signs + +. Tremor +. Thyroid moderate soft, symmetrical enlargement.

She has had prolonged roentgen-ray treatment. Our observations cover the last half of this course only. No change occurred in metabolism, pulse rate or weight during this time, though clinically she appeared to be a little better.

CASE 72.—Miss E. P. (O. P. D. 286790, X-Ray 676). Duration, one month. Slightly toxic. Eye signs +. Tremor +. Thyroid, slight symmetrical enlargement. Faint bruit.

She was observed only twice. This year she writes that she is in good health.

CASE 77.—Mrs. S. I. R. (W. M. and W. S. 210686). Duration, two and one-half years. Very toxic. Eye signs +. Tremor + +. Thyroid, moderate soft symmetrical enlargement. Loud bruit.

She died following a lobectomy.

CASE 89.—Miss M. S. (O. P. D. 300446, X-Ray 817). Duration, eighteen months. Slightly toxic. Eye signs + +. Tremor +. Thyroid, moderate soft symmetrical enlargement. Loud bruit.

She was observed during roentgen-ray treatment, under which she showed no definite improvement. Her present condition could not be learned.

CASE 93.—Mrs. A. B. (W. M. and W. S. 212531, X-Ray 968). Duration, two months. Slightly toxic. Eye signs +. Tremor +. Thyroid, slight soft symmetrical enlargement. Moderate bruit.

She was observed through a course of roentgen-ray treatment which had no apparent effect. She was operated on later, recovered promptly, and has remained well for two years. When seen this year she had no signs or symptoms of exophthalmic goiter. Her metabolism was normal and she was doing housework for a family of four.

CASE 100.—Miss McH. (W. M. 211450). Duration, seventeen months. Slightly toxic. Eye signs +. Tremor +. Thyroid, right lobe palpable. No bruit.

She had had fifteen roentgen-ray treatments before we saw her. She has not been seen this year, but her doctor writes that she has recovered.

CASE 114.—Miss O. S. (O. P. D. 314339, X-Ray 962). Duration, three years. Moderately toxic. Eye signs + + +. Tremor +. Thyroid, marked soft symmetrical enlargement. Bruit present.

She was observed during a course of roentgen-ray treatments. She recovered promptly. When seen this year she presented moderate exophthalmos, but no other signs of exophthalmic goiter. Her metabolism was normal and she was working to full capacity.

CASE 121.—Miss M. M. (E. M. 212253, W. S. 214295, X-Ray 1021). Duration, one year. Very toxic. Eye signs +. Tremor + +. Thyroid, moderate soft symmetrical enlargement. Moderate bruit.

This patient had the highest metabolism of any in the series. She has been studied very completely from the start to the present time. A course of roentgen-ray treatments, together with complete rest, brought her metabolism from +118 to +58 per cent., with only a slight fall in pulse rate, and no gain in weight. After lobectomy her metabolism promptly fell to +15 per cent., with a corresponding fall in pulse. This year she had a metabolism only 11 per cent. above normal and was apparently cured. She received three more roentgen-ray treatments after operation. She had a barely perceptible exophthalmos. She had been working for two years as a domestic.

CASE 130.—Miss K. L. (E. M. 212770). Duration, six weeks. Moderately toxic. Eye signs +. Tremor + + +. Thyroid, moderate soft symmetrical enlargement. Loud bruit.

She showed a definite improvement on rest alone. Later she was operated on in an outside hospital. This year she writes that she is not improved.

CASE 131.—Mrs. S. J. G. (E. M. 229863, X-Ray 1067). Duration, five months. Slightly toxic. Eye signs +. Tremor +. Thyroid, slight fullness. No bruit.

When seen this year, after two years of essentially no treatment, she showed a slight fall in metabolism and pulse rate, gain in weight and slight general improvement.

CASE 138.—Mr. C. J. (O. P. D. 320460). Duration, six years. Moderately toxic. Eye signs + + +. Tremor + +. Thyroid not enlarged.

He was observed for two months only, during which time he took essentially no treatment and showed no change. His present condition could not be learned.

CASE 139.—Mrs. R. K. (O. P. D. 195120, X-Ray 1051). Duration, four years. Slightly toxic. Eye signs + +. Tremor +. Thyroid, moderate soft symmetrical enlargement. Loud bruit.

She was observed twice during roentgen ray treatment. There was no great change in her condition. Her present condition could not be learned.

CASE 144.—Mrs. H. (W. M. 213327). Duration, two years. Slightly toxic. Eye signs +. Tremor +. She had a hemithyroidectomy at the Peter Bent Brigham Hospital in 1914. The remaining lobe of the thyroid was slightly enlarged.

Present condition unknown.

CASE 156.—Theodore D. (W. M. 213713, X-Ray 1060). Duration, five months. Moderately toxic. Eye signs + + +. Tremor + +. Thyroid, moderate soft symmetrical enlargement. Moderate bruit.

A boy with moderately severe exophthalmic goiter, had four roentgen-ray treatments and this year was much better. All signs and symptoms of thyrotoxicosis were less marked.

CASE 160.—Mr. K. (E. M. and W. S. 213989). Duration, two months. Moderately toxic. Eye signs + +. Tremor + +. Thyroid, moderate soft symmetrical enlargement. Moderate bruit.

She got more toxic in spite of complete rest in bed and died after lobectomy.

CASE 161.—Mrs. C. M. (E. M. 213880, W. S. 217740). Duration, eight months. Moderately toxic. Eye signs + +. Tremor +. Thyroid, moderate asymmetrical enlargement. Moderate bruit.

She showed a slight fall in metabolism on rest in bed and died later following a lobectomy.

#### INTERPRETATION OF DATA

To interpret the data set forth in the preceding tables properly is somewhat difficult. We have sought, by using the basal metabolism as an index of toxicity, to determine the exact effect of roentgen-ray therapy and partial thyroidectomy on the course of exophthalmic goiter. Confusing factors always arise, however. The factor of rest, for instance, or that of drugs, keeps coming in to complicate the picture, as does that of the tendency to spontaneous recovery. Having found that rest alone usually causes the metabolism to fall, we must take great care in attributing observed improvement entirely to surgery or to the roentgen ray. In experimental animals one could study a single factor at a time. This cannot be done with patients if we have proper regard for their welfare. Nevertheless, the present studies bring out a number of interesting points, which we will discuss in turn.

The data of the various cases differs in completeness. It would have been highly desirable if each case had been observed at definitely fixed intervals. This has not been possible. Some patients have been more than willing to come for observation whenever we wished. Others who do not live near Boston have sometimes been able to come only at long intervals. In order to draw conclusions as to the result of treatment, therefore, we have had to separate the cases into groups, each group illustrating some one point.

For purposes of interpretation we have constructed a diagram (Fig. 1). In this are shown, the effect of rest alone, that of rest plus quinin hydrobromid, that of surgery and that of roentgen-ray treatment. The diagram shows average results, represented as columns. To illustrate the effect of rest, for example, we have taken the figures for all cases where observations were secured before and after a period of rest in bed, and averaged the metabolism before and after. The columns represent these averages. The same thing has been done in regard to rest plus quinin hydrobromid. As a matter of fact, these two points are taken directly from Tables 1 and 2 of our first paper.<sup>2</sup>

The data concerning the effect of the roentgen ray has been handled as follows: First, the cases that had been observed before and after roentgen-ray treatment were tabulated, as in Table 3 of our first paper. We then made the following groupings: Group 1, observations secured after from one to two treatments; Group 2, after from three to five treatments; Group 3, after from six to seven

treatments; Group 4, after ten or more treatments, and Group 5, from two to three years after the fifth treatment. These groups were composed for the most part of observations on the same patients, but sometimes, for example, we had observations on a patient to include in Groups 1 and 3, but not in Groups 2 or 4. In a preliminary diagram we arranged five pairs of columns, the first of each pair representing the average metabolism of the group before treatment, the second after treatment. In the diagram actually shown there is but one "before" column which is the average of the five "before"

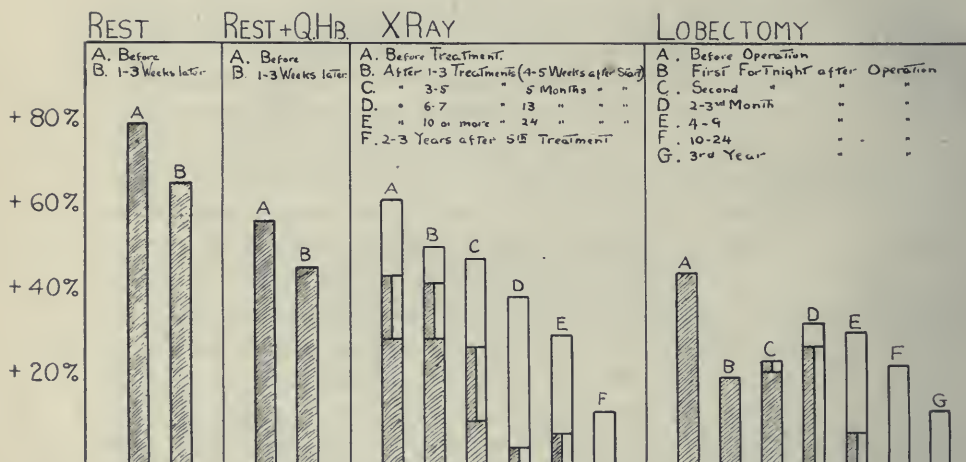


Fig. 1.—Diagram showing average metabolism levels and effect of various sorts of treatment thereon. The columns indicate the percentile increase above the standard. The cases composing each average are enumerated in the Appendix. The method of constructing the diagram is explained in the text. The shading indicates what proportion of the patients forming any average were receiving complete rest (full shading), partial rest (half shading), and what proportion were leading their usual lives (unshaded).

columns of the five groups. The five "after" columns have been reduced to this average "before" column by a simple proportion:

$$B : A = B_2 : A_2$$

in which  $B$  = the actual "before" column of the group,  $B_2$  the average "before" column, and  $A$  = the actual "after" column of each group, and  $A_2$  = the reduced "after" column shown in the diagram.

This method, while somewhat cumbersome, was rendered necessary by discrepancies in the sequence of observations. However, it finally gives us a satisfactory curve of the effect of the roentgen ray on the largest group of cases available. We did not include in this curve those cases where our first observation was secured only after they had already had roentgen-ray treatment.

The surgical data has been handled in identically the same manner. A statement of exactly what cases were included in the formation of any of the columns in Figure 1 is given in the Appendix.

As we have mentioned before, the factor of rest continually comes in to obscure our deductions. In the diagram, therefore, we have indicated by shading what proportion of the cases were receiving complete or partial rest, and what proportion were leading their usual life.

*Effect of Rest.*—The first two columns in the diagram show that a group of cases observed at the beginning of a period of complete rest in bed had an average metabolism of +81 per cent., and that after from one to three weeks the same group had an average of +67 per cent. A study of the individual metabolism curves of the several cases shows that this drop is a very common, though not inevitable, occurrence. In a few of the more toxic cases, the curve rose in spite of complete rest. It will further be seen on such study that the fall is not progressive. After a time a level is usually reached, and rest alone will not cause a further drop. There is not a single patient in the series whose metabolism was brought to within normal limits by rest alone. These remarks apply to rest in bed over periods of weeks. They do not apply necessarily to rest extending for months or years. We have no observations on the effect of such prolonged rest.

*Effect of Quinin Hydrobromid.*—We have not studied the action of quinin hydrobromid thoroughly, nor over any long period. Its action when added to that of complete rest over periods of from one to three weeks is shown by the second pair of columns in the diagram. The average metabolism of this group before taking the drug was +58 per cent. and after taking the drug it was +47 per cent., a fall no greater than that accomplished by rest alone.

*Effect of Roentgen Ray.*—The series of roentgen-ray observations are distinctly interesting. The first column, that before treatment was begun, shows an average metabolism of +63 per cent. At that time a little less than half the patients were getting complete rest, a little less than one-fourth were getting partial rest, and the remainder were following their normal mode of life. The second column, that after one or two treatments, shows a reduction to +52 per cent. for the group, with relatively rather more of the patients getting complete rest than in the first. After from three to five treatments there is a slight drop, and after six or seven treatments there is a greater drop, with rest playing a lesser and lesser part. Finally, two or three years after the fifth treatment, the group average metabolism is only +13 per cent. and all the patients are leading normal lives.

Under roentgen-ray treatment, then, the group, as a whole, showed a progressive improvement as measured in terms of the metabolism.

*Effect of Surgery.*—The group average before lobectomy was + 46 per cent. At that time all the patients were getting complete rest in bed. During the first fortnight after operation there is a very extraordinary fall to + 21 per cent. The next two columns, however, show a secondary rise up to the fourth month after operation. From then on there is a progressive fall, until in the third year the average is + 13 per cent. and all the patients are back leading normal lives. The marked fall in the metabolism immediately after lobectomy, followed by a secondary rise, is very common, though not, as will be seen by studying the individual curves, invariable. It may be due in part to the disturbance caused by the patients leaving the hospital and returning home, but this is not the sole cause, for some increase occurs while they are still in the wards.

*Roentgen-Ray Therapy and Surgery Compared.*—In the third year, after treatment was well established, the end results in the surgical and roentgen ray groups are identical, namely group averages of + 13 per cent. in each case, with all patients leading normal lives. With the roentgen ray group the improvement was gradual but progressive; with the surgical group there was a sudden marked improvement and a subsequent relapse. The factor of rest was distinctly greater in the surgical group than in the roentgen ray group, yet no more ultimate benefit was, apparently, secured. Moreover, before treatment was begun, the roentgen ray group had a much higher average toxicity than the surgical group, there being an increase in the metabolism of 63 per cent. in the former as against 46 per cent. in the latter. However, since all the surgical cases were resting before operation, while only a part of the roentgen ray cases were resting, the surgical group might be thought to be actually composed of more severe cases than the roentgen ray group. As a matter of fact, this is not true, however, for the highest metabolism observed in the former group, before the rest period had started, gives an average of only + 61 per cent., which is lower than that of the roentgen ray group before treatment.

It would seem to us, from a study of these results, that the chance of cure in exophthalmic goiter is as good with roentgen-ray treatment as with surgery, in groups of cases of equal toxicity, and that being true, the former method is the preferable, for the danger of fatal outcome is less. Of the nine known deaths occurring in our original series of fifty-five cases, five were directly the result of surgery (Cases 23, 52, 77, 160 and 161). One patient (Case 10) after prolonged roentgen-ray treatment finally died apparently of exoph-

thalmic goiter. Three patients died of unknown causes; one of these (Case 126) after having apparently been cured by operation, one (Case 21) after having apparently been cured by the roentgen ray, and one after failure to improve materially under roentgen-ray therapy (Case 113).

We have given due consideration to the matter of the possible relationship of duration to the improvement in the roentgen ray and surgical groups. It must be admitted that there is a very definite tendency toward spontaneous recovery in exophthalmic goiter. To what extent the improvement in our two groups must be attributed to the natural course of the disease is an unanswerable question. The average duration of the roentgen-ray group in the spring of 1919 was about five and one-half years, while that of the surgical group was about three and one-quarter years. Whether the longer duration in the roentgen-ray group was an important factor in their progress, we cannot say. The lack of relation between duration and end result in individual cases makes it seem unlikely.

*Relation of Metabolism to Other Factors.*—Up to the present point our discussion has hinged almost entirely on the basal metabolism. The clinical progress, however, has been indicated in the tables. Before closing, it will be well to consider briefly the relation of metabolism to other factors, such as body weight and pulse rate. The respiratory quotients, the blood picture and pathologic findings we intend to study further, and if anything of interest is found it will be reported later.

We have already indicated in our earlier paper<sup>2</sup> that between the basal metabolism and the clinical picture there is a close parallelism. Subsequent observations have for the most part borne this out, although there are occasional exceptions.

To see what, if any, relationship there is between metabolism, weight and pulse, we have plotted these factors in all cases in which five or more observations have been secured. It is not worth while to encumber the present paper with these charts. It may be said, however, that in about 60 per cent. of the cases so charted, there is a close parallelism between pulse and metabolism, and in the remainder a certain amount of parallelism. This is what one would expect, and indicates that in any given case the resting pulse rate is a tolerably good index of the patient's progress. The pulse rate, however, gives comparative results only, for between the metabolism elevation and pulse elevation of different individuals there seems to be but little relationship. The pulse rate, therefore, is not an index of the absolute degree of intoxication in the patient seen for a single time, but it does furnish a relative index in a patient seen at different times.

One would also suppose that the curve of body weight would also bear a definite relationship to the metabolism curve, that when the metabolism fell the weight would increase, that, in other words, the curves would be reciprocal. In about 20 per cent. of the cases there is some evidence of such a reciprocal relationship, but in the rest there is not. Indeed, in some cases we find the exact opposite, the weight increasing with a rising metabolism and vice versa.

The matter of the relationship of metabolism elevation to blood sugar has been discussed by one of us (J. C. A.) in an earlier paper.<sup>23</sup> We have restudied these sugar curves in the light of the present end result data to see whether any information of value in prognosis could be got from the height of the hyperglycemia. No constant relationship of sugar curve to end result could be demonstrated.

*Metabolism as a Guide to Treatment.*—One may ask, what is to be learned from these studies in regard to the indications for treatment in exophthalmic goiter?

In the first place, as just stated, it seems clear that the majority of patients ultimately do as well with roentgen-ray therapy as with surgery, and that with less hardship to themselves. This being true and in view of the not infrequent fatal outcome of surgical operations on the thyroid, the roentgen-ray form of treatment would seem to be the method of choice. We do not mean by that that surgery is never indicated. Such cases as No. 93 and No. 121 that failed to improve under roentgen-ray therapy and promptly recovered after operation prove that surgery may be necessary. It will, however, be interesting to note in this connection that of a total of twenty-four patients who were operated on, nine had had more or less roentgen-ray treatment before surgery was done. In our diagram the group of columns illustrating the effect of the roentgen ray includes only those patients who received roentgen-ray treatment and rest alone; the group of columns showing the effect of surgery, on the other hand, includes patients who had had roentgen-ray treatment before operation. In this connection we should also like to call attention to the fact that none of the five patients who died following operation had received<sup>24</sup> roentgen-ray treatment beforehand. It is further interesting to note that in the ten postoperative cases in which we have from two to three year end result observations, the basal metabolism of five patients who had roentgen-ray treatments before operation (Cases 71, 88, 93, 121 and 143) averaged +6 per cent., while that of five patients who were operated on without previous roentgen-ray treatment<sup>24</sup> (Cases 106,

23. Denis, W., and Aub, J. C.: Blood Sugar in Hyperthyroidism, Arch. Int. Med. 20:964 (Dec.) 1917.

24. This statement is not absolutely true, for a few of these patients had received one roentgen-ray treatment before operation. A single treatment, however, is not of great moment and can be disregarded.

125, 129, 148 and 151) averaged +20 per cent. The metabolism of the former group of five averaged +44 per cent. before operation and that of the latter +50 per cent. While the two groups started about evenly, therefore, at the end of two years the group in which surgery was preceded by roentgen-ray treatment showed a far better result than the group in which surgery alone was done.

In view of all this, it seems clear that not only should the roentgen ray be tried first in the management of exophthalmic goiter, with the idea that it may be sufficient to cure the patient, but also because if not alone sufficient to cure, it may render subsequent operation safer, and more likely to be followed by good end results. Surgery, we believe, should be employed with conservatism, and usually only after the roentgen ray and other medical measures have failed. We also believe that after operation, if the metabolism remains elevated, the roentgen ray should again be employed. A case in point is that of (Case 99) Miss M. T. P. with whom no great fall in metabolism was secured by operation but who later definitely improved under roentgen-ray treatment.

In this connection we wish to state that we believe that the roentgen-ray treatment of the thymus is quite as important as that of the thyroid. In the cases that come to operation it seems possible that the safety imparted by previous roentgen-ray treatment is due in some measure to the effect on the former gland.

Numerous writers have felt that the sudden deaths following operations on the thyroid were of thymus origin. Kocher,<sup>25</sup> Halsted<sup>9</sup> and others have performed thymectomies with favorable results. Klose<sup>26</sup> and others have shown that involution of the thymus follows irradiation. Treatment of the thymus by the roentgen ray, therefore, to our minds, should form a part of the pre-operative treatment of exophthalmic goiter. Exposure of the thyroid, we believe, should also be carried out. That roentgen-ray exposures of the thyroid render operations much more difficult through the production of adhesions between gland and capsule, is denied by Dr. C. A. Porter.<sup>27</sup>

Can we now go a step further, and find in these metabolism studies anything that enables us to predict what patients probably will come to operation, and in which ones operation is contraindicated? We believe we can.

A study of the relation of pulse curve to metabolism curve in individual cases shows two fairly definite types: Type 1 in which

25. Kocher, T.: Die Behandlung der Basedowsche Krankh., München. med. Wchnschr. **13**:680, 1910.

26. Klose, H.: Beiträge zur Pathologie und Klinik der Thymusdrüse, Jahrb. f. Kinderh. **78**:653, 1913.

27. Porter, C. A.: Personal Communication.

the pulse rate (when plotted in a uniform way with a base line of a pulse rate of fifty and a normal metabolism, and a top line of a pulse rate of 150 and metabolism + 100 per cent.) runs ten or more points above the metabolism curve, and Type 2 in which the pulse curve coincides with, or runs below, the metabolism curve.

Eppinger<sup>28</sup> gives an extreme tachycardia as one of the characteristics of the sympatheticotonic type, while a moderate tachycardia occurs in the vagotonic, and that latter type is presumably that in which there is most pronounced thymus involvement. Without entering into the discussion as to whether two such types actually exist, it occurred to us that it would be well to compare the end results in those of our cases that had an extreme tachycardia and a moderate metabolism elevation on the one hand (Type 1) with those that had an extreme metabolism elevation and a moderate tachycardia (Type 2) on the other hand. For this purpose, belonging to Type 1, we have Cases 66, 71, 88, 93, 110, 135, 143 and 129, and belonging to Type 2, Cases 33, 48, 121, 123, 125, 148 and 151. A study of the end results in these cases shows that the patients of Type 1 did about equally well with surgery or roentgen ray alone, or with surgery preceded by roentgen-ray treatment, while with Type 2 surgery alone gives poor results, the roentgen ray alone may cure, but the roentgen ray followed by surgery may be necessary in the more resistant cases.

Of the five patients who died following operation, four (Cases 23, 52, 160 and 161) belonged to Type 2, and only one (Case 77) belonged to Type 1. The chance of postoperative death, therefore, seems greater in Type 2, at least when roentgen-ray treatment has not been given beforehand.

An apparent contraindication to operation was found in a metabolism rising in spite of the fact that the patient was getting complete rest in bed at the time.

#### CONCLUSIONS

The conclusions drawn in our first paper are borne out by subsequent work. In addition, we should like to say that using the basal metabolism as an index of toxicity in exophthalmic goiter we have found that:

1. In the majority of cases the results after two or three years are equally good with roentgen-ray treatment as with surgery.
2. That after surgery the metabolism shows a rapid preliminary fall, a secondary rise followed by a final fall, that with roentgen-ray treatment there is a gradual progressive fall.

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28. Eppinger, H., and Hess, L.: *Vagotonie, Sammlung Klinischen Abhandlungen über Pathologie und Therapie der Stoffwechsel von Noorden*, Nos. 9 and 10, Berlin, 1910.

3. That in securing the same end results with surgery or with the roentgen ray, a lesser rest factor is necessary with the roentgen ray. With the roentgen ray there is practically no mortality. With surgery there is a definite one.

4. That patients treated surgically do better, and the risk of operation is less, if they have previously had their thyroid and thymus glands irradiated.

5. That the risk of operation is greater and the need for pre-operative roentgen-ray treatment is greater in cases with a very high metabolism and moderate tachycardia than in those with an extreme tachycardia and moderate metabolism elevation.

6. That the safest program for the treatment of exophthalmic goiter, as a whole, is the routine irradiation of thyroid and thymus glands, in all cases, with surgery held in reserve for patients who do not then do well.

7. That surgery is contraindicated with patients whose metabolism is rising in spite of complete rest in bed, and also with patients of the type with moderate tachycardia and great metabolism increase, except when they have previously had thyroid and thymus glands treated by the roentgen ray.

8. Finally, we believe that in the management of exophthalmic goiter, periodic determination of the basal metabolism should be quite as much a routine as is the examination of the urine for sugar in diabetes mellitus. Further, that in borderline cases the basal metabolism furnishes very valuable aid in differential diagnosis.

15 Chestnut Street.

## APPENDIX

The columns shown in Figure 1 are made up of observations on various cases as follows:

Rest Series: Cases 10, 88, 111, 121, 137, 151.

Quinin Hydrobromid Series: Cases 3, 77, 99, 117, 126, 130, 131, 135, 160, 161.

Roentgen-Ray Series:

From one to two treatments.—Cases 10, 21, 48, 93, 110, 111, 113, 120, 121, 123, 131, 135.

From three to five treatments.—Cases 21, 25, 33, 53, 66, 93, 107, 110, 111, 113, 120, 121, 123, 156.

From six to seven treatments.—Cases 12, 25, 33, 48, 53, 66, 110, 123, 135.

Ten or more treatments.—Cases 10, 48, 66, 111.

From two to three years after the fifth treatment.—Cases 33, 48, 66, 110, 111, 123, 135.

Surgical Series:

First fortnight.—Cases 71, 83, 88, 93, 117, 121, 125, 126, 137, 143.

Second fortnight.—Cases 3, 88, 93, 99, 106, 117, 125, 126, 143, 151.

Second and third months.—Cases 71, 83, 88, 93, 99, 106, 117, 125, 126, 130, 137, 143.

From fourth through ninth month.—Cases 71, 88, 99, 106.

From tenth through twenty-fourth month.—Cases 3, 16, 88, 93, 126.

Third year.—Cases 71, 88, 93, 106, 121, 125, 129, 143, 148, 151.

# THE MORE COMMON GASES; THEIR EFFECT ON THE RESPIRATORY TRACT

OBSERVATION ON TWO THOUSAND CASES

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CHICAGO

Recent medical literature, both domestic and foreign, relative to the effect on the respiratory system of the various gases employed as part and parcel of the chemical warfare in the war has been rather meager. Especially is there a scarcity of information regarding a study of gas cases in their chronic stage. With the aid of a bibliography from the surgeon-general's library, we have combed over carefully foreign and domestic relative matter, and were able to find comparatively little. It is with a degree of temerity and hesitancy, therefore, that this (pioneer) work is undertaken. I experience a certain amount of moral courage, however, in confining myself solely to observations and clinical findings, and in avoiding conclusions. The clinical data embodied in this paper are based on the observation of about two thousand cases studied in the capacity of review examiner on the medical examining board at Camp Grant, Ill.

Under the present war department regulations, all gassed soldiers coming up for discharge, irrespective of the presence or absence of symptoms or findings, are referred by the general heart and lung examiners to the board of review for disposition. In an atmosphere of quiet, these men are examined thoroughly and the degree of disability, and the amount of compensation determined. Since Dec. 1, 1918, approximately two thousand such cases have been referred to the review board at Camp Grant, and of them this paper will attempt a classification, comparative study, and a few original observations and deductions.

In determining the type of gas to which the individual soldier was subjected, we have been obliged to place a great deal of dependence on the personal history. The overseas records in many instances merely attested to the fact that the soldier had been gassed, and gave the length of his stay in the hospital. However, we have found the matter of history very reliable. The average soldier evidences a lively interest in himself and in his condition, and is able not only to name the type of gas with which he was affected, but gives a connected intelligible description of his early and late symptoms. So that the element of conjecture and uncertainty is quite negligible, and after careful ques-

tioning, we feel reasonably certain of the correctness and authenticity of our classification.

As is quite generally known, gassing occurred in one of two distinctly different ways. The first, which was most common in the early days of the war, was through the medium of a gas attack — the laying down of a barrage followed by a "gas cloud." This gas cloud or "drift gas," as it was originally known, consisted of chlorin, or chlorin plus a synthetic compound. As the war progressed, drift attacks for diverse reasons were modified and to a more or less degree replaced by high explosive gas shells. In our observation of two thousand cases, we encountered 240 men who sustained their gas poisoning through cloud or drift gassing, the remainder through high explosives. The gasses of the high explosive shells were of several varieties. We have prepared a table for the comparative study of these gasses and have divided the table into two distinct groups. Group 1 includes those men who sustained their poisoning through cloud or drift attacks, the type of gas being chlorin; Group 2 includes the remainder, all those subjected to high explosive gassing. This latter group includes mustard gas as the most important numerically, chlorin as equally important because of its severity and toxicity, phosgene, chloropicrin and a mixed gas. Our table offers not only a list of gases encountered with the number of cases in each list, but offers also a comparative study of the severity of each type, the symptoms complained of, the length of hospitalization of the individuals. The more important gases will be gone into in detail, chlorin being given the greatest attention, because of its frequency and severity. Just a word at this time about the information gathered through a comparative study of the effects of chlorin gas in Groups 1 and 2. The table shows unmistakably that cases of chlorin gas poisoning in Group 1, the men subjected to cloud attacks, were more severe, called for longer hospitalization, showed more extensive physical findings, and threatened a more protracted convalescence than did the chlorin cases of Group 2, the men subjected to chlorin through high explosive shells.

*Chlorin.*—We have singled out chlorin for a more detailed study and discussion for several reasons. In the first place, except for mustard gas, which represented more than 30 per cent. of all our cases, chlorin was the most common type encountered. Mustard gas, while it affected the lungs very markedly, and in many cases produced interesting respiratory physical findings, must, nevertheless, be considered a surface gas rather than a pure inhalatory type gas. In the second place, chlorin gas cases presented a history and subjective symptoms of greater severity and longer duration and longer hospitalization, and physical examination of the men, on an average of four months after

the attack, showed more real palpable findings than did any other type of gas poisoning encountered.

The average gas case appearing before the review board at Camp Grant was in the chronic stage of disease, having sustained the attack on an average of from three or four months prior to the final examination, consequently we are forced to depend for a description of the acute stage on the recent medical literature covering that phase of the subject. Monographs covering the early course of gas cases are both prolific and thorough. We have selected one entitled, "Lecture on Gas Poisoning," by Hill,<sup>1</sup> and will quote freely from his paragraphs on symptoms and pathology.

Under symptomatology, Hill says: "The typical case is cold, with a subnormal temperature, pulse is slow and full. The face is cyanosed and the posture is one gasping for breath. The respirations are jerky, often numbering forty a minute, associated with a choking cough and a frothy expectoration. With each inspiration the chest is expanded to its fullest, all the auxiliary muscles being brought into play. This first is the asphyxial stage which usually lasts about thirty-six hours. This stage is followed by symptoms of bronchitis. There is a greenish mucopurulent expectoration, high temperature, small rapid pulse (160), and the respirations are shallow and fast (60). Diminished expansion is one of the most pronounced physical findings at this time, and is due, we thought, to the contraction of the bronchial tubes."

Speaking of prognosis, Hill says: "There seems no reason why recovery of the lungs should be any less perfect after chlorin poisoning than it is after bronchopneumonia." Hill concludes his paragraph on prognosis with these words: "I have no evidence to offer as to the state of the lungs at any long period after the poisoning." That experience we have had in abundance at Camp Grant. Our work began where Hill left off. Hill saw the patient in the acute stage, we saw him in the chronic stage. Hill studied the subject from one to four days after the attack, we had him under observation from three to four months later. Our findings and conclusions are recorded elsewhere in this paper. We agree with Hill in his statement on prognosis. We, too, feel that there is no apparent reason why these subjects should not regain normal respiratory function and rid themselves of their gradually disappearing symptoms.

For the pathology on gas poisoning, we are also dependent on the literature. While the mortality in acute cases was high, and consequent necropsies were numerous, conversely the mortality in the chronic cases is negligible and necropsies sparse. The morbid anatomy records

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1. Hill, L.: *J. Roy. Army Med. Corps*, London **26**: (Jan.) 1916.

of the acute cases are in keeping with the physical findings. Hill describes his postmortem findings as follows: "The mucosa of the trachea and larger bronchi shows intense congestion. The lungs do not collapse in these acute cases, but appear like a solid cast of the thoracic cavity, and are greatly increased in weight. On incision, the lung tissues appear of a deep maroon red color, and the exudation flows from the cut surface in abundance. Light gray patches are to be seen on the surface of the lung amidst the congested areas. They were found to be due to emphysema. So intense is the obstruction to the entry of air, and so violent the efforts of respirations, that emphysema is produced in these least poisoned parts where air can still enter. The parts of the lung not affected by emphysema show intense congestion of the capillaries, and many of the alveoli are seen filled with exudate. Death is probably brought about by stasis in the pulmonary vessels."

GROUP 1. GAS SUSTAINED IN CLOUD OR DRIFT ATTACK

No.	Chlorin	Mustard	Phosgene	Chloropierin	Mixed	Time in Hospital	Cough	Findings
240	240	...	...	...	...	4 months	60%	8%

GROUP 2. GAS SUSTAINED THROUGH HIGH EXPLOSIVE GAS SHELLS

280	280	...	...	...	...	3 months	25%	3%
741	...	741	...	...	...	11 weeks	20%	4%
186	...	...	186	...	...	9 weeks	28%	3.5%
33	...	...	...	33	...	5 weeks	17%	1.5%
515	...	...	...	...	515	10 weeks	23%	3%

Total 2,000

It will be seen that the necropsy findings just enumerated coincide in detail with the physical findings elicited even after four months of the disease (which are considered in a later paragraph). We have been able to map out distinctly patches or areas of diminished breath sounds and an accompanying tympanitic percussion note which undoubtedly correspond with an underlying area of stretched and dilated alveoli—an emphysema. Before leaving the subject of morbid anatomy in chlorin gas cases, we wish to quote the report on a post-mortem examination of a German prisoner of war who died from the effects of chlorin poisoning. The case is reported by Crabbe,<sup>2</sup> and emphasizes what has already been said: "Postmortem: The patient was gassed September 25, presumably by chlorin or some chlorin compound. When admitted to the Base Hospital he was slightly cyanosed and had a yellowish toxic appearance. The respirations were on the average 60, and the pulse rate 120. There was some rise of

2. Crabbe: J. Roy. Army Med. Corps, London 26: (Jan.) 1916.

temperature. The symptoms were more toxic than bronchitic, the cough was not severe. He died October 4, at 8 a. m.

"Postmortem: Pleura adherent both sides and base; adhesions easily broken down; no fluid in the pleura. Lungs appeared to be distended with marked emphysema. On section they showed marked emphysema and particularly toward the apices; the bases were congested. There was a general purulent bronchitis with marked increase of pus towards the apices. The bases were cyanosed. The contained blood was almost black, but the coagulability was below normal. Both lungs floated, also sections from apex and base.

"Trachea: The mucous membrane was coated with mucopus and infected, the infection increasing toward the bifurcation. There were old glands at the bifurcation."

Here, again, we not only have the necropsy findings of emphysema and bronchitis to correspond with similar physical findings, but we find a complete agreement in detail. The patches of emphysema detected in physical examination are shown in the necropsy room, and the preponderance of bronchial râles at the bases and over the large bronchial trunks, are shown to emanate from the moisture collected there. In chronic gas poisoning, therefore, and more specifically in chronic chlorin gas poisoning, as evidenced by physical findings, corroborated by necropsy, we are dealing with a pathology of one of two distinct varieties: (1) Bronchitic; (2) emphysematous, or (3) a combination of the two.

A comparative study of the history and early symptoms of the three most frequent and most important gases, mustard, chlorin and phosgene, reveals some interesting differences.

*Mustard Gas.*—Perhaps the most frequent and most pronounced early symptom of mustard gas poisoning complained of by the soldier is that of hemorrhage and bleeding from the nose. We are astonished at the frequency with which that symptom was given as the most annoying of the early results of mustard gassing. Cough, shortness of breath, sneezing and other signs of irritability of the air passages were included in the anamnesis, but hemorrhage held first place. With many it seems to have been very mild, in some instances merely a frothy blood tinged sputum or inconsequential epistaxis; in others, a true hemorrhage of such magnitude, that it must have caused concern to the individual as well as the army surgeon in charge.

*Chlorin Gas.*—Almost as prominent as the history of hemorrhage in mustard gas, is the complaint of a suffocation, a distressing inability to get enough air, in chlorin gas poisoning. These patients complained of cough, a few of hemorrhage, but the important universal early symptom experienced was in effect a sense of constriction around the

chest, a tightness in the throat, and a panting for breath. This condition lasted from twenty-four to seventy-two hours; and gave way to a chronic cough, with general irritability of the air passages.

*Phosgene Gas.*—Patients suffering from phosgene gassing complained of cough, bloody sputum, sneezing, but mainly of weakness—a general weakness which came on as early as two hours after gassing, and as late as three days, and lasted for weeks and even months. Long after the cough had disappeared, this weakness remained.

*Physical Findings.*—The physical findings of any or all of our two thousand gas cases at an average period of four months after the attack will admit of a fairly nice classification into three groups:

1. Normal Group: The apparently normal group, as the table will show, includes almost 50 per cent. of the total. A careful thorough physical examination fails to reveal any abnormalities. Expansion is normal, the breath sounds are clear and vesicular. The percussion note is negative and there is no moisture. And in the face of these apparently normal physical findings, there is oftentimes a complaint of cough, shortness of breath on exertion, all of which presents a disconcerting problem. With the complaint of respiratory distress and without definite physical findings, and no apparent pathology, we have no guide toward a logical prognosis.

2. Bronchitic Group: This group includes practically 30 per cent. of all cases examined. The findings are rather definite, and do not differ materially from the subacute and chronic bronchitis ordinarily encountered. The type of breathing is harsh and high-pitched throughout. Expiration is prolonged and at times interrupted, most pronounced after exercise. Moisture is abundant. There are coarse, moist râles rather evenly distributed, most pronounced over the bronchial trunks and at the bases, occasionally fine, moist râles in the apices which disappear on coughing. When we remember that these findings are in evidence as long as five months after the acute onset, we are impressed with the toxicity of the initial irritant action on the mucous membranes of the respiratory tract, and we are apt to conjecture on the probable duration of the findings and the ultimate result.

3. Emphysema Group: The third group, which included about 22 per cent. of our two thousand cases, was characterized by the presence of an emphysema. On inspection, the chest seemed moderately rigid, the movements of the diaphragm limited, expansion impaired, and the accessory muscles in use. On palpation tactile fremitus was markedly diminished, and in some instances entirely absent. On percussion, a hyper-resonant note was detected. On auscultation the breath sounds over the entire chest, except the bronchial area, were

much diminished and faint. In some cases we were able to map out discrete patches of emphysema.

In confirmation of the physical findings just enumerated, we found in a paper by Elliott<sup>3</sup> the following: "On physical examination one notes a marked limitation of movement of the apices of the lungs. The chest seems fixed as in an old emphysema. The respiratory murmur is usually faint above and below the clavicular area, though at times harsh in the infraclavicular. The adventitious sounds are variable, but when present are those of a bronchitis or bronchiolitis.

*Prognosis.*—In considering the prognosis of a disease or condition in which marked subjective symptoms are contrasted with meager or entirely absent physical findings, we are seriously handicapped, and our conclusions must be more or less conjecture. This is especially so if we are denied the help of past experience. In our review of two thousand gas cases we are confronted with just this difficulty. Nevertheless, we have after careful individual and group examination and comparison, arrived at rather definite conclusions:

1. That gas victims, irrespective of the type of gas and severity of attack sustained, show no marked predisposition toward active pulmonary tuberculosis, or toward the reactivation of a healed or quiescent pulmonary lesion.
2. That gas victims present little evidence of material destruction of lung tissue.
3. That gas victims with emphysema findings have a more protracted convalescence than have those of the bronchitic group.

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3. Elliott, J. H.: *Internat. J. S.* (Dec.) 1918.

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